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THE PARTIAL PANCREATECTOMY

INVESTIGATIONS REGARDING EXPERIMENTAL CHRONIC PANCREATIC DIABETES

BY

EINAR LANGFELDT

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From the University Physiological Institute (Professor Dr. S. Torup),
Christiania.

The Partial Pancreatectomy.

Investigations regarding experimental chronic pancreatic diabetes.

By

EINAR LANGFELDT.

Preface.

This work has been executed at the University Physiological Institute in Christiania between the summer of 1916 and the summer of 1918.

For the help that has been afforded me by the principal of the institute, Professor Dr. med. S. Torup, both in the planning of the work and in connection with the operations I beg hereby to offer Professor Torup my most sincere thanks.

The microscopical investigations have been carried out at the University Anatomical Institute. I beg the principal of the institute, Professor Dr. med. K. E. Schreiner, to accept my most sincere thanks for the kindness he has shown in placing at my disposal working-room and appliances and for his friendly guidance in the judging of the microscopical preparations.

I desire also to express my gratitude to Dr. med. H. Chr. Geelmuyden for his guidance in connection with the literature of diabetes.

Christiania, 15th May 1919.

Einar Langfeldt.

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Introduction.

The result of v. **Mehrings** and **Minkowskis** total extirpation of the pancreas in 1889 (1) was highly surprising for contemporary physiologists. From the first experiments in extirpation made by **Brunner** in 1673 (2) till the later essays commenced by **Claude Bernard** (3) and continued by **Berard** and **Colin** (4), **Senn** (5), **Finkler** (6) and **Martinotti** (7) it was usual to regard the pancreas as an organ that could be removed without any appreciable injurious consequences to the organism. It was therefore found difficult to ascribe to the pancreas itself so remarkable an influence on the entire metabolic process as v. **Mehring** and **Minkowski** could now record.

These latter found that the total extirpation was followed by a glucosuria occurring in immediate succession to the operation and by a metabolic condition that much resembled diabetes mellitus, and which resulted in death in the course of 2 or 3 weeks. They also found that, if quite small remnants only of the pancreas tissue were left behind, no diabetes appeared, provided that the portions left behind were sufficiently nourished and not necrosed. In those cases in which diabetes occurred after incomplete extirpation they never found on dissection any trace of pancreas tissue. They therefore concluded that only the complete absence of pancreas tissue was capable of inducing diabetes, but they emphasise the importance it would have for judging about the functions of the pancreas, if after partial extirpations, where large portions of the pancreas were left behind, diabetes should arise after some time. [(1) p. 382.]

Experiments in this direction were made by **Sandmeyer** in 1892 (8).

He operated on 2 dogs. In one of them he left behind $^1/_6$, in the other $^1/_9$ of the pancreas. The former got spontaneous glucosuria on an protein-diet 13 months after the operation, the latter 4½ months after. This glucosuria, in contrast to the glucosuria after v. MEHRING's and MINKOWSKI's total extirpation, took a *chronic course.* In reality there developed a chronic diabetes. The first dog lived for still 8 months, the second for 2 months.

A short time previously MINKOWSKI (9) after partial extirpations, leaving behind $^1/_8$ to $^1/_{12}$ of the gland, had observed slight degrees of diabetes in succession to the operation in the form of alimentary glucosuria after sugar and bread [loc. cit. p. 114 and p. 115]. None of these dogs were under observation for a longer period than a few weeks. Either the rest of the pancreas was then removed, and the animal succumbed to gallopping diabetes, or else the animal was killed. SANDMEYER let his dogs live, and chronic diabetes developed. In the course of this diabetes investigations were made regarding the passage of the different carbohydrates into the urine in the form of glucose and regarding the effects of feeding with pancreas.

Whilst v. MEHRING's and MINKOWSKI's experimental results had soon been confirmed by many investigators [(10) II, p. 344], they were far from meeting with general adhesion for their opinion that the cause of the glucosuria was to be sought for in the cessation of a definite function of the pancreas, a function which had by MINKOWSKI (9) been assigned to an internal secretion of the pancreas. There was general scepticism. It was only slowly and by degrees that doubt gave way before the incontestable evidence of the experimental results.

CLAUDE BERNARD's classic works (3) (11) on the influence of the nerve-system still engaged all minds and thoughts, and no analogies were known with regard to other organs.

The matter assumed quite a different complexion, when at the end of the last and in the beginning of the present century the teaching about the endocrine functions demonstrated the most remarkable influences on the part of the different organs.

In spite of these analogies and notwithstanding that the pancreas was now acknowledged to be an organ with internal secretion, yet there were still some physiologists who maintained the nerve-hypothesis as explaining the occurrence of glucosuria. PFLÜGER, especially, strongly defended that theory (12—19), (26). PFLÜGER held that glucosuria was due to a lesion of the duodenal nerve-plexus, and he also observed glucosuria after extirpation of the duodenum in a frog. MINKOWSKI (20), however, was able to prove that in a dog the duodenum could be totally extirpated without revealing any disturbance in carbohydrate-metabolism. In the end PFLÜGER's objections were held to be without any justification. But they had, nevertheless, been of service in giving occasion for investigations of decisive importance in determining the function of the pancreas.

By degrees, however, it became clear that also several of the other endocrine organs exerted an influence on carbohydrate-metabolism. Extract of adrenal, thyroid gland and hypophysis were capable of inducing glucosuria in normal individuals, while on the other hand in case of hypofunction of these organs it was thought that an increased glucose-tolerance could be observed.

The consequence of these investigations was that the pancreas lost the sovereign position independent of the other organs with respect to the genesis of glucosuria which otherwise would have been assigned to it. It was now by degrees assigned a more passive role, a mainly restrictive influence on the activity of the organs mentioned in mobilising the carbohydrates (EPPINGER, FALTA and RUDINGER) (157).

With respect to *Diabetes mellitus* these same views have in the main prevailed. The conception of the originating causes in this disease has followed in the footsteps of experimental research since CLAUDE BERNARD's demonstration of the importance of the nerve-system down to the latest investigations regarding the influence of the endocrine organs on carbohydrate-assimilation.

As regards the relationship of genuine diabetes mellitus to the pancreas, an affection of the pancreas has never been generally recognised as a cause of this disease. The pathological-anatomical changes have been too variable and uncertain; and as regards the experimental results, the diabetes induced by the total extirpation of the pancreas corresponds perhaps at most to the very rare cases of acute diabetes in human beings, but it gives no data for the understanding of chronic diabetes. FALTA (117), (71) rightly emphasises the great difference in the metabolism in pancreatic diabetic (total-extirpated) dogs and in human diabetics, and he points out especially the lower D/N quotient, the enormous nitrogen excretion in hunger and the usual absence of ketonuria in such pancreas-diabetic dogs as contrasted with the higher D N quotient, the scarcely increased nitrogen excretion in hunger and the considerable ketonuria met with in diabetes mellitus.

A condition that arises so suddenly and is so rapid in its course as the total pancreatic-diabetes would seem, moreover, to be ill-suited for comparative investigation in connection with a disease so chronic in its course as diabetes mellitus.

For such investigations the chronic diabetes after partial extirpation of the pancreas as described by SANDMEYER seems to be more suitable.

The results of the metabolic experiments which SANDMEYER during a long time carried out on his dogs show, however, little conformity with the metabolic conditions in genuine diabetes mellitus. The D/N quotient is low and ketonuria is absent. (Nitrogen excretion in hunger was not investigated.)

In the course of the years that have elapsed since SANDMEYER's publication this chronic diabetes has not found many new investigators. Not before 1910 were observations similar to those made by SANDMEYER published by THIROLOIX and JACOB (33), (34), (35). They found that partial extirpation of the pancreas, leaving behind from $^1/_5$ to $^1/_6$ of the portion around the main excretory duct, induces forms of diabetes characterised by absence of emaciation and by the long duration of the disease. The animal can absorb up to 80 % fat and assimilate a certain quantity of glucose. Two forms of diabetes can be produced by this mode of procedure: A rapid form (type d'emblée), in which the glucosuria is constant and progressive, and in which the animals die in a marastic state after from 3 to 6 months, and a slower form (type différée) of from 13 to 18 months duration. After a temporary loss of weight the animals increase in weight and are apparently normal. In the course of from 5 to 8 months there is only a decrease in carbo-hydrate tolerance. Ingestion of quite small quantities of food containing carbo-hydrates occasions a rapid increase of blood-sugar and severe glucosuria. The glucosuria disappears on a meat-diet. Later on, continued feeding with carbo-hydrates produces permanent glucosuria with emaciation.

On dissection they found the remnant of the pancreas in good condition, the other endocrine organs normal. Only in the liver might changes be found: enlargement, fatty-degeneration, sclerosis [(35) p. 377—378].

With partial extirpation of the pancreas, but without leaving behind such large portions as mentioned by THIROLOIX and JACOB, ALLEN (22) has also been able to produce slighter forms of diabetes with a period of decreased tolerance for glucose preceding the appearance of the spontaneous glucosuria.

None of these investigations yield any enlightenment on the features of metabolism, which are of significance for understanding the relationship between the experimental pancreatic-diabetes and diabetes mellitus.

Such metabolic investigations are, however, necessary in order to make clear that relationship. The similarity noticeable in the progress of the glucosuria itself permits of no conclusions regarding the metabolism. There is, moreover, the difficulty, that normally the metabolism of dogs is divergent from that of human beings. This divergency is revealed, for instance, in the fact that dogs, unlike human beings, do not get acidosis and ketonuria in hunger. However, according to VON NOORDEN [(42) p. 201], by putting normal dogs for a long time on a diet rich in carbo-hydrates and afterwards allowing them to starve, it is possible to produce acidosis and ketonuria in them also. With a suitable diet containing abundance of carbohydrates it would therefore appear to be possible to alter the metabolism of the animals used for experiment, so that it would become more like that of human beings. Dogs with such a »transformed« metabolism might be assumed to be more suitable as subjects for experiment than ordinary meat-eating dogs in investigations regarding experimental pancreatic-diabetes.

Neither have any of the investigations hitherto made given any enlightenment, as to how the experimental chronic diabetes *develops* out of a normal carbo-hydrate-metabolism. It is clear that it would be of the greatest importance for understanding the part played by the pancreas in the development of diabetes if, after partial extirpation of the pancreas which is not followed by spontaneous glucosuria, and in the beginning perhaps not even by decreased tolerance for glucose, a gradual transition from a normal to pathological carbo-hydrate metabolism could be shown.

The simplest method of investigating this question is to examine the glucose-tolerance. In an eventual decrease in tolerance for glucose after partial extirpation of the pancreas, or in a decrease appearing in the course of the development, one can find figures indicating the altered metabolism, and at the same time trace the very earliest signs of the developing diabetes.

In order to be able to judge the results of such tolerance-tests it is necessary to know the determining conditions for glucosuria. An insight into these conditions will be obtained through examination of the amount of blood-sugar present during tolerance-tests on normal and on depancreatised animals.

It will also be of interest, by varying the operative methods and by using both puppies and full-grown animals, to investigate to what extent the different parts of the pancreas and the age of the animal are of significance.

As to the anatomical basis for the internal secretion of the pancreas, whether it is to be sought for in the islands of Langerhans, in the acini, or both in the islands and in the acini, opinions have long been divided.

An exact anatomical examination of subjects for dissection, especially if one had at one's disposal partially depancreatised animals, some of which had contracted diabetes and others not, would contribute to the solution of this question, and an investigation of the other endocrine organs would perhaps afford data for judging of the influence of these organs on the diabetic condition.

Keeping these considerations in view the design of this work has been by means of systematically executed tolerance-tests to investigate how the glucosuria arises and develops after partial extirpation of the pancreas in dogs of different ages, and with which an attempt has been made to render the metabolism more similar to that of human beings by means of a diet rich in carbo-hydrates and free from meat, and secondly by varying the methods of operation to investigate the question, whether the removal of different parts of the pancreas has any significance.

In the next place the object has been to examine from a metabolic and clinical standpoint the occurrence of chronic diabetes, giving special consideration to those points which are of importance for comparing this condition with the genuine human diabetes mellitus.

As the concluding portion of the task comes an anatomical investigation of the materials obtained by dissection.

The work therefore naturally falls into 3 divisions:

1. *Development of glucosuria.*

Under this heading are recorded the results of the operations, the results of the tolerance-tests and of the investigations regarding the blood-sugar, as well as the other observations regarding carbo-hydrate-metabolism during this period.

2. *The manifest diabetes.*

Under this heading comes the description of the clinical picture and of the metabolic changes which appeared spontaneously during the progress of the chronic diabetes. There are further recorded the results of the investigations made regarding the special questions concerning the metabolism.

3. *Post-mortem findings.*

Development of Glucosuria.

In this chapter are recorded the results of the systematically executed tolerance-tests after partial extirpation of the pancreas. As a change in the carbo-hydrate metabolism would find its expression in an altered glucose-tolerance, it was necessary by means of experiments on normal animals also to investigate how the latter stood with regard to such tests, and furthermore to have constantly at hand in the course of the investigations control-animals to show the normal conditions.

General Methodics.

1. Subjects for Experiment.

In order that the results of the tolerance-tests after partial extirpation of the pancreas should be of any value it was necessary that both the animals operated on and the control-animals should belong to the same litter, and that they should have lived the whole time under the same conditions. All the dogs used for these tests came to the laboratory as quite small pups, 6 weeks old. With a view to transforming their metabolism and thereby perhaps rendering possible the development of a condition resembling as closely as possible the genuine diabetes mellitus, the dogs received a diet very rich in carbo-hydrates, and outside of the tolerance-tests they never got meat. They all had the same diet of bread and milk. Also after the operation the animals operated on got the same diet as the normal animals, until the spontaneous glucosuria arose.

A litter of 4 deerhound pups was secured. Three of them were operated on, the fourth was the control-animal. Afterwards a litter of foxterriers, of which one was operated on, the other was control-animal.

2. Operation-technics.

Twenty-four hours before the operation the animals got the last meal, after which they were bathed.

The narcosis was begun with chloroform and afterwards continued with chloroform-ether. The abdomen was shaved from the costal arc downwards. Afterwards a washing with alcohol and with ether. Desinfection with tincture of iodine. The animal and surroundings were covered with sterilised towels. Otherwise ordinary asepsis as in cases of laparatomy. For ligatures and sutures there was employed exclusively linen-thread, which had been boiled for 1 hour.

Incision in the middle line between the proc. xiph. and umbilicus. The strongly developed subserous fat-tissue was shoved aside, and the omentum lifted up. The pylorus-duodenal angle was sought for with the fore-finger, whereupon the duodenum with the adhering pancreas was lifted out through the opening of the incision. The pancreas of the dog is then found to be an angular body consisting of a horizontal portion (cauda pancreatis), generally longer and often thicker, extending over towards the milt (processus lienalis) and a vertical portion (caput pancreatis) with the upper, thickest part (corpus) fastened to the duodenum and the lower part (processus uncinatus) not fastened to the duodenum, often thinner and ending in a point.

The extirpation was always begun from the free ends of the pancreas, the mesentery being tied piece by piece and doubly. In removing the parts adhering to the duodenum any lesion of the pancreatico-duodenal vessels common to the duodenum and pancreas was carefully avoided. This the most difficult and important part of the operation was executed with the greatest caution, in the first place to avoid necrosis of the duodenum and in the second place in order to preserve the circulation of blood in the remnant of the pancreas. Likewise the biliary ducts were carefully spared. Whenever duodenal remnants of the pancreas were left behind, it was always the parts around the excretory ducts. These parts were ligated distally in such a manner, that the remnants of the pancreas had a normal discharge for excretions. Before any resection of the pancreas was attempted, or before any pancreas-tissue at all was removed, double ligature was always carried out. After resection the duodenum was restored to its position, and the omentum again spread over the intestines.

Suturing layer by layer of the peritoneum, of the fasciae and musculature and of the skin.

The wound was covered with a collodiumbandage.

3. Analytical Methods.

The urine was examined qualitatively for sugar by means of FEHLING's, WORM-MÜLLER's and ALMÉN's tests. When the result of WORM-MÜLLER's reaction was negative the phenylhydrazin-test was always made, likewise when the result was not doubtless positive, the osazone was always produced.

The sugar contents were determined quantitatively by polarization before and after fermentation and by BANG's micromethod.

Nitrogen was determined after KJELDAHL's method.

Ammonia after FOLIN's method.

The test for *aceton* and *acetic acid* was made qualitatively by means of LIEBEN's and GERHARDT's reactions.

The total aceton content was determined according to MESSINGER-HUPPERT.

The blood-sugar was determined by BANG's micromethod.

The methodics employed in the tolerance tests with glucose and the metabolic methodics for the special metabolic investigations are recorded separately in their respective sections.

Glucose-tolerance in normal dogs.

The glucose-tolerance in normal dogs has been investigated by a number of experimenters by means of intravenous, subcutaneous and intraperitoneal injections of glucose, and by administration per os and per rectum.

Intravenous injections on dogs have been performed by DOYON and DUFOURT (159), by BLUMENTHAL (160) and by BOERI and DE ANDREIS (161). *Subcutaneous* injections by SCOTT (162), UNDERHILL & CLOSSON (21), ALLEN (22). *Intraperitoneal* injections by SCHMIDT & MEYER (23) and ALLEN (22). Injections *per rectum* by EICHHORST (24).

The results arrived at by these experimenters with the different methods vary in the case of each method just as much as the results arrived at with administration per os, which will be dealt with later on. And the reasons for these divergent results in the former cases must be assumed to be the same as in the last-named method, namely: that in one and the same main method the conditions and technics of the experiments are various. The results will therefore not be comparable. And this holds good in a still greater degree for the different methods of administering the glucose. The differences are here so profound and essential that comparisons between their respective results are impossible.

The glucose-tolerance in normal dogs with administration per os has been investigated by several experimenters. There is, however, little agreement between the results obtained. While one investigator has found the tolerance very low [HOFMEISTER (25)], and others have easily been able to produce glucosuria with comparatively small quantities of glucose [BOERI & DE ANDREIS (161), QUARTA (27)], other experimenters have found a very high tolerance [SCHLESINGER (29), DE FILIPPI (28), PRATT & SPOONER (30), ZANDA (31)], so that large doses of glucose were required to produce glucosuria, or else glucosuria could not be produced at all [PFLÜGER (26)].

HOFMEISTER (25) ascertained the glucose-tolerance in 4 dogs. The first contracted glucosuria after administration of from 1,9 to 2,5 g. glucose per kg., the second after 2,9 g. per kg., the third after 5,8 g. per kg. The fourth on the other hand did not contract glucosuria after 4 g. per kg. HOFMEISTER's dogs were small, the smallest weighing 1,9 kg., the largest 3,4 kg. They were all female dogs. The glucose was given dissolved in varying quantities of meat broth, now and then with the addition of some meat.

PFLÜGER (26) failed to produce glucosuria in 2 normal dogs after doses of 11,4 and 12,1 g. per kg. The glucose was given together with minced-meat and water. In the case of 2 dogs, in which the duodenum had been excised, glucosuria could not be produced even after doses of 17 g. and 21,3 g. per kg.

Between these extreme limits, which have thus been established by HOFMEISTER and PFLÜGER, lie the figures that have been found by the other experimenters.

BOERI & DE ANDREIS (161) established the limit of tolerance at from 4 to 6 g. per kg., when the animal was fasting, and at from 10 to 13 g. when the glucose was given with other food.

QUARTA (27) found an average tolerance-limit of 4,06 g. per kg. for male dogs and of 10,28 g. per kg. for female dogs. The glucose was given together with meat and bouillon.

DE FILIPPI (28) gave glucose to 2 dogs in a 20 % solution of water by means of the stomach-tube without any contemporary nourishment. In one of the dogs there appeared traces of sugar in the urine after 10 g. per kg., in the other none.

SCHLESINGER (29) found the tolerance-limit different according to the size of the animal. Small dogs contracted glucosuria more easily than large ones. Whilst the smaller dogs (5 kg.) got glucosuria after doses of 8 g. per kg., the larger dogs (8 kg.) did not get glucosuria after from 10 to 12 g. per kg.

PRATT & SPOONER (30) found the tolerance-limit to be very high. In 4 different dogs glucosuria was not produced by doses of from 9,8 to 15,6 g. per kg.

ZANDA (31) failed to produce glucosuria with doses of up to 12 g. per kg.

It will at once be seen that the results which the experimenters mentioned have arrived at are not comparable. Apart from the fact that the dogs employed are different with respect to size, age, condition of nourishment and sex, the technics of investigation adopted by the different experimenters are extremely divergent. Some of them administered the sugar on an empty stomach, others did not. The sugar was given in soup, in water, in mince-meat. Even one and the same investigator has not adopted the same technics in all his experiments. And, finally, as regards the actual presence of the glucosuria itself, it may now and then be doubted, especially in the case of the older investigators, whether it was really sugar that they found, when it is a question of a trace discovered by reduction-test.

The variations in technics, experimental conditions and results will be revealed by the following tabular statement. Where anything is not recorded in the table, information on that point is lacking in the case of the author in question.

Author	Size	Age	Sex	Glucose given with	State of stomach	Tolerance	Glucosuria indicated by
Hofmeister . .	1,9 to 3,4 kg.	various	female	meatsoup		1 to 2,5 g. per kg.	Worm-Müller's reaction
Pflüger . . .	7,9 to 12,4 kg.			Mince-meat	empty	more than 11,4 to 12 g. per kg.	W.-M.
Pflüger . . .	12,4 kg.			bouillon	empty	more than 8,0 g. per kg.[1]	W.-M.
Boeri & de Andreis					empty	4,6 to 6 g. per kg.	
Boeri & de Andreis				meat		10 to 13 g. per kg.	
Quarta			female	meat & bouillon		10,28 g. per kg.	
Quarta			male	meat & bouillon		4,06 g. per kg.	
De Filippi . .	12,25kg.	adult	male	water	empty	10 g. and more than 10g.perkg.	W.-M.
Schlesinger .	5 kg.					8 to 9 g. per kg.	
Schlesinger .	8 kg.					10 to 12 g. per kg.	
Pratt & Spooner	5,3 to 13,3 kg.		male & fem.	meat & water, and some fat	empty	9,8 to 15,6 g. per kg.	Fehling's reaction
Zanda	6 to 10 kg.			water	partly empty	more than 12g.perkg.	Fehling

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[1] In the Table (loc. cit. page 21) stands »green reaction, disappeared after fermentation, polarisation ÷ 0,1.« Pflüger understood »green reaction« as positive result of Worm-Müller's reaction. After our present knowledge of the matter [Geelmuyden (32)] this is not the case.

From these earlier investigations regarding glucose-tolerance in normal dogs it will appear that the manner in which the glucose is administered sets its stamp upon the result in a higher degree than any other factor. It will therefore be necessary to consider closely what method of administration ought to be adopted, when it is a question of determining the tolerance. The following considerations are of weight in this connection: The accuracy of the method, frequency of the tests, duration of the experiments, effect on the general health, and the possibility of complications.

As regards accuracy, that is to say, when it is question of introducing with certainty a definite quantity of glucose into the organism of the animal, subcutaneous and intravenous injections hold decidedly the highest rank. Also as regards facility in execution these methods are not inferior to, for instance, the oral method by means of the stomach-tube. On the other hand, they will be less serviceable, when the tests are made frequently, and when the experiments are to extend over a long period of time, months and years. Moreover, there is the increased possibility of complications in the form of infection, as well as an influence on the general health that may be very undesirable. Nevertheless, these methods have their supporters. ALLEN [(22) p. 57], recommends the subcutaneous test in the following words: »For animals it is the best of all methods and should be adopted as the standard procedure. It is harmless, highly convenient and accurate.« DE FILIPPI [(28) p. 549], is of a quite different opinion. He maintains that tolerance-tests by injection of sugar-substances, whereby the latter are introduced into the circulatory system with avoidance of the liver, are uncertain and that objections can be brought against them which are perhaps of greater force than those that can be made against administration by natural channel. DE FILIPPI draws attention to the fact that in the case of subcutaneous injections evidence is lacking as to the rapidity with which the sugar is absorbed, and as to the completeness of its passage into the circulatory system. In this connection it is stated that it has happened that LIEBIG's Extract of Meat, subcutaneously injected, has lain for several weeks in the subcutaneous connective tissue without being absorbed. As regards direct injection into the veins the same author asserts that in this case the matter is still more complicated.

The rapidity with which the injection is carried out has its influence, and likewise the operative methods employed in rendering the animal immobile. And, finally, the pharmacological, toxic effects produced by the introduction into the circulatory system of large quantities of sugar must be taken into consideration.

These objections, which have also their justification in case of extraperitoneal and to some degree in case of rectal injections, will have still greater weight, when it is question of investigations that are to be carried out on the same animal during months or years. The method that will then present itself as most expedient is the oral. If the sugar is introduced by means of the stomach-tube, this method is quite equal to the injection methods with respect to accuracy. And as it has no effect on the general health, as the possibility of complications is very slight, and as the tests can be made daily, this method has distinct advantages over all others in case of long-continued investigations. And, finally, there is the far from unessential point that the sugar by this method enters into the organism in a quite natural manner, that the conditions of absorption and assimilitation are normal and that the observations that are made under these circumstances will be better adopted for the physiology and pathology than observations made under conditions more divergent from the normal.

In view of these considerations administration of the sugar per os was the method adopted in these investigations.

Before proceeding to speak of the special methodics it will be necessary to clear up the *terminology* employed in connection with tolerance-tests under physiological and pathological conditions. »Limit of assimilation«, »co-efficient of utilisation«, »limit of repletion» are the terms that have been employed by the different authors to designate the observations that can be made in tolerance-tests. None of these expressions are coextensive in meaning with each other. Neither is it possible to fix upon a single designation, seeing that there are 2 fundamentally different manners of determining the tolerance.

Either we can ascertain the lowest limit for the occurrence of the glucosuria, that is to say: the smallest quantity of glucose that is capable of inducing glucosuria; or we can ascertain the largest quantity of glucose that the organism can assimilate. The latter method leads to a result only in the case of diabetic individuals, who after a certain limit quantitatively excrete all surplus sugar. Among non-diabetics no such upper limit is to be found; the capacity for assimilating increasing doses, even if these doses in themselves induce glucosuria, is practically unlimited.

It seems therefore necessary to have a designation for each of these phenomena. In the following pages the expression »*tolerance*« will be employed to designate the smallest quantity of glucose that is capable of inducing glucosuria and the expression »*assimilation-capacity*« to designate the largest quantity of glucose that the organism is capable of assimilating.

In normal indivuals (non-diabetic) the tolerance is therefore to be determined, in diabetic individuals both the tolerance and the capacity of assimilation.

The methodics in the tolerance-tests on normal as well as on operated dogs were as follows:

Twenty-four hours after the last feed (the animals were fed only once every day) the sugar was administered by means of a stomach-tube in a 20 % solution. Glucose from Merck, puriss.—tested for purity by polarisation and titration. On the days when the tolerance-tests took place the diet otherwise consisted only of minced horse-flesh. The minced-meat was given 3 hours after the sugar. The dog was kept in a metabolic cage, and the urine was collected during the course of 24 hours. In the beginning catheterisation was employed. This was abandoned later on as being superfluous, as it turned out that all sugar was excreted after 6 hours, and the urine passed after that time was free from sugar.

1. Tolerance-test on young animals.

Dog III.

Foxterrier, female, $3^1/_2$ months old.

Came into the laboratory 6 weeks old. Has lived all the time exclusively on bread and skimmed milk.

Table 1.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenyl-hydrazin test	
$^{9}/_{5}$	3,05	440	—	—	$^{8}/_{5}$ 30 g. glucose, 200 g. minced horse-flesh, 150 g. bread.
$^{10}/_{5}$	2,95	490	—	—	$^{9}/_{5}$ 40 g. glucose, 200 g. minced horse-flesh. 150 g. bread.
$^{11}/_{5}$	3,00	190	—	—	$^{10}/_{5}$ 50 g. glucose, 200 g. minced horse-flesh.
$^{12}/_{5}$	3,05	260	—	—	$^{11}/_{5}$ 60 g. glucose, 200 g. minced horse-flesh.
$^{13}/_{5}$	3,10	190	—	—	$^{12}/_{5}$ 70 g. glucose, 200 g. minced horse-flesh.
$^{14}/_{5}$	3,17	300	—	—	$^{13}/_{5}$ 80 g. glucose, 200 g. minced horse-flesh,
$^{15}/_{5}$	3,15	290	—	—	$^{14}/_{5}$ 90 g. glucose, 200 g. minced horse-flesh.
$^{16}/_{5}$	3,25	310	—	—	$^{15}/_{5}$ 100 g. glucose, 200 g minced horse-flesh.

We began with 10 g. glucose per kg. No glucosuria. The dose was daily increased by 10 g. up to 100 g. (30,7 g. per kg.) without glucosuria appearing (Table 1). This dog was afterwards operated.

Dog VI.

Foxterrier, male, $3^{1}/_{2}$ months old, of same litter as the preceding. Came into the laboratory at the same time and was fed in the same way. Served afterwards as control-animal for the preceding.

Table 2.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenyl-hydrazin test	
$^{9}/_{5}$	3,30	300	—	—	$^{8}/_{5}$ 30 g. glucose, 200 g. minced horse-flesh.
$^{10}/_{5}$	3,20	455	—	—	$^{9}/_{5}$ 40 g. glucose, 200 g. minced horse-flesh.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenyl-hydrazin test	
$^{11}/_{5}$	3,12	175	—	—	$^{10}/_{5}$ 50 g. glucose, 200 g. minced horse-flesh.
$^{12}/_{5}$	3,15	230	—	—	$^{11}/_{5}$ 60 g. glucose, 200 g. minced horse-flesh.
$^{13}/_{5}$	3,30	215	—	—	$^{12}/_{5}$ 70 g. glucose, 200 g. minced horse-flesh
$^{14}/_{5}$	3,35	260	—	—	$^{13}/_{5}$ 80 g. glucose, 200 g. minced horse-flesh.
$^{15}/_{5}$	3,42	240	—	—	$^{14}/_{5}$ 90 g. glucose, 200 g. minced horse-flesh.
$^{16}/_{5}$	3,50	340	—	—	$^{15}/_{5}$ 100 g. glucose, 200 g. minced horse-flesh.
$^{17}/_{5}$	3,50				$^{16}/_{5}$ 125 g. glucose, 200 g. minced horse-flesh. Vomiting.

The attempt to produce glucosuria had the same negative result as with the first dog. The dog received 100 g. (28,5 g. per kg.) without getting glucosuria (Table 2). On the attempt being made to introduce larger quantities vomiting occurred

Dog V.

Deerhound, female, 4 months old.

Came into the laboratory 6 weeks old. Was fed the whole time exclusively on bread and milk.

Table 3.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenyl-hydrazin test	
$^{31}/_{10}$ 1916	4,40	410	—	—	$^{30}/_{10}$ 28,7 g. glucose (6,5 g. per kg.) 250 g. minced horse-flesh.

Table 4.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenyl. hydrazin test	
13/12 1916	7,55	920	—	—	12/12 80 g. glucose (0,6 g. per kg.) 500 g. minced horse-flesh.
14/12	7,70	1,040	—	—	13/12 100 g. glucose (13,50 g. per kg.) 500 g. minced horse-flesh.
15/12	7,75	1,200	—	—	14/12 120 g. glucose (15,50 g. per kg.) 500 g. minced horse-flesh.
16/12	7,75				15/12 150 g. glucose, 500 g. minced horse-flesh Vomiting after half an hour.

The dog tolerated up to 120 g. glucose (15,50 g. per kg.) without getting glucosuria (Tables 3 and 4). Larger doses occasioned vomiting. This dog served as control-animal for the others of the same litter, on which partial extirpation of the pancreas was performed. The results of the tolerance-tests are recorded later on under the respective experiments.

Thus, in these dogs it was not possible to produce glucosuria, even with the largest doses the animals were capable of retaining.

2. Tolerance-test on full-grown animals.

Dog VII.

Setter, male, full-grown.

Came to the laboratory 2 weeks before the beginning of the experiment. It has lived mainly on a meat diet.

Table 5.

Date	Weight kg.	Urine			Glucose g. Bang	Remarks
		quant. ccm.	reduction tests	phenylhydrazin test		
$^{21}/_{11}$	15,50	550	—	+	0,82	$^{20}/_{11}$ 100 g. glucose, 700 g. minced horse-flesh.
$^{22}/_{11}$	15,60	610	—	—		$^{21}/_{11}$ 100 g. glucose, 700 g. minced horse flesh.

At the first experiment the dog got glucosuria after 100 g. glucose (6,4 g. per kg.). The sugar-excretion was, however, small and could not be determined polarimetrically. On repetition of the experiment next day it did not get glucosuria (Table 5).

Dog V.

Previously tested when a puppy. The dog's age at the time of experiment was 1 year and a quarter, It had lived all the time on bread and milk.

Table 6.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenylhydrazin test	
$^{6}/_{11}$ 17	11,55	880	—	—	$^{5}/_{11}$ 100 g. glucose, 500 g. minced horse-flesh.

As was the case a year before, the dog remains free from sugar after 100 g. glucose(now equal to 8,7 g. per kg.) (Table 6).

Dog IV.

Deerhound, female, 9 months old. Belongs to the same litter that came into the laboratory 6 weeks old. Has previously got only bread and milk.

Table 7.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenyl. hydrazin test	
$^{13}/_{4}$ 17	13,60	1325	—	—	$^{12}/_{4}$ 150 g. glucose (11 g. per kg.) 600 g. minced horse-flesh.

150 g. glucose (11 g. per kg.) did not produce glucosuria. (Table 7).

Dog VI.

Foxterrier, male, $1^{1}/_{4}$ years old. Previously tested when a puppy.

Table 8.

Date	Weight kg.	Urine			Remarks
		quant. ccm.	reduction tests	phenyl. hydrazin test	
$^{4}/_{6}$ 18	9,00		—	—	$^{3}/_{6}$ 100 g. glucose (11,11 g. per kg.) 500 g. minced horse-flesh.
$^{6}/_{6}$	9,00		—	—	$^{5}/_{6}$ 100 g. glucose, 500 g. minced horse-flesh.

Glucosuria cannot be produced this time either. (Table 8.)

Of these tolerance-tests carried out on normal dogs only one produced glucosuria. The dog that got glucosuria was the only one that had previously lived mainly on a meat-diet. All the other dogs, which did not get glucosuria even after the largest doses it was possible for the animal to retain (up to 30,7 g. pr. kg.), had lived on a diet rich in carbohydrates, only bread and milk. How far such a previous mode of life is of significance cannot be decided from these experiments. But it is proved *that dogs, both young and full-grown, have an extraordinarily high glucose-tolerance.* The object of these experiments was to obtain control-tests for the subsequent tolerance-tests on operated dogs. None of the control-animals contracted glucosuria. As actual control-animals can be reckoned only those that came to the laboratory as puppies at the same time as those afterwards operated on, belonging to the same litter and living the whole time under the same conditions and on the same diet as the latter.

Glucose-tolerance after partial extirpation of the pancreas.

As mentioned in the introduction, Minkowski had already ascertained a decreased tolerance for glucose after operations that left behind from 1/8th to 1/12th of the pancreas. In the case of a dog in which there had been left behind 3 cm. of the outermost point of the vertical portion of a pancreas 32 cm. long alimentary glucosuria was produced after 20 g. of glucose, whilst the dog remained free from sugar after 500 g. meat plus 100 g. bread [(13) p. 114 and p. 115]. A few weeks later the dog was re-operated, and the remnant of the pancreas removed, whereupon it got rapid diabetes.

Both of Sandmeyer's dogs showed decreased tolerance for starch given in the form of bread immediately after the operation (loc. cit.). Both of them had a slight diabetes the whole time. These dogs did not go through any stage characterised by glucosuria after glucose but not after starch, and still less any stage with normal carbo-hydrate-metabolism.

Thiroloix and Jacob [loc. cit. (35)] make no mention of having observed such a stage. Small quantities of carbo-hydrates immediately occasioned an increase in the concentration of blood-sugar and extreme glucosuria.

Allen [loc. cit. p. 1003] has observed decreased tolerance for glucose after partial extirpation of the pancreas with subcutaneous and oral administration in periods where glucosuria did not appear after bread and meat. There is no record of systematic investigations carried out during a long period of time.

In the following chapter such systematic investigations shall be described.

1. **Tolerance-tests after operation on young animals.**

Dog I.

Deerhound, male.

This dog belongs to a litter of deerhounds, 4 in all, which came into the laboratory 6 weeks old. Since coming in it has lived exclusively on bread and milk.

At the time of the operation it is $3^1/_2$ *months old* and weighs 3.70 kg.

Operation $^{16}/_{10}$ *1916:* The whole of the horizontal portion and the point of the vertical portion were removed. The pieces removed were 15 cm. long and weighed 12 g. There was left behind a piece of the duodenal part (caput) around the excretory ducts. The piece left behind was $1^1/_2$ cm. long and was estimated as being 1/9th of the whole gland. (Fig. 1.)

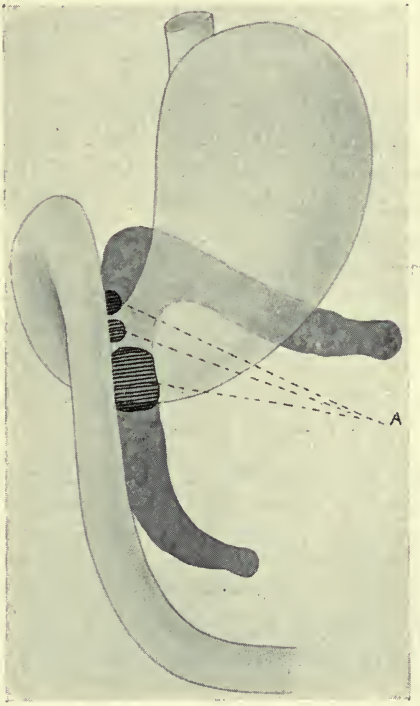

Fig. 1. Dog I. A — Remnants of pancreas left behind.

The dog stood the operation well. It got no glucosuria, even after a meal rich in starch (150 g. dog-biscuits = 90 g. carbohydrates). On the other hand it got glucosuria after milk. (See protocols).

Table 9.

10 days after the operation the first tolerance-tests were made:

$^{25}/_{10}$:	weight	3.6	kg.	—	Per os	5	g. glucose.	Urine:	no glucosuria.
$^{26}/_{10}$:	»	3.65	»	—	» »	7	» »	»	no glucosuria.
$^{27}/_{10}$:	»	3.7	»	—	» »	10	» »	»	no glucosuria.
$^{29}/_{10}$:	»	3.8	»	—	» »	20	» »	»	1.19 g. glucose (Bang)[1]
$^{30}/_{10}$:	»	3·85	»	—	» »	25	» »	»	5.21 g. glucose »

The nourishment otherwise consisted of 250 g. minced horseflesh daily, given 3 hours after the glucose.

The limit for the occurrence of glucosuria was 20 g. glucose corresponding to 5.2 g. per kg. of weight of body. (Table 9.)

Control-test.

Dog of same litter, female, not operated. Weight 4.4 kg.

$^{31}/_{10}$: 28.7 g. glucose (6.5 g. per kg.). Urine: *no glucosuria.*

The dog operated on was taken out of the metabolic cage and afterwards received daily 200 g. household bread and half a litre skim-milk.

The tolerance-tests were now repeated with 10 days' interval.

Table 10.

$^{10}/_{11}$:	weight	5.05	kg.	—	Per os	27	g. glucose.	Urine:	no glucosuria.
$^{11}/_{11}$:	»	5.05	»	—	» »	32.5	» »	»	6.49 g. glucose.

Nourishment otherwise 300 g. minced horse-flesh daily.

The tolerance has increased. No glucosuria after 27 g. glucose (5.2 g. per kg). (Table 10).

Table 11.

$^{22}/_{11}$:	weight	5.70	kg.	—	Per os	39	g. glucose.	Urine:	2.05 g. glucose.
$^{23}/_{11}$:	»	5.70	»	—	» »	39	» »	»	2.09 g. glucose.

After another 10 days 39 g. glucose (6.5 g. per kg.) produces slight glucosuria. (Table 11.)

Table 12.

3/12:	weight	6.9	kg.	—	Per os	45.5	g. glucose.	—	Urine:	no glucosuria.
4/12:	»	7.0	»	—	» »	45.5	» »	—	»	no glucosuria.
5/12:	»	7.17	»	—	» »	60.	» »	—	»	2·66 g. glucose.
6/12:	»	7.30	»	—	» »	60.	» »	—	»	2.65 g. glucose.
7/12:	»	7.40	»	—	» »	80.	» »	—	»	7.22 g. glucose.
8/12:	»	7.50	»	—	» »	80.	» »	—	»	7.09 g. glucose.
9/12:	»	7.75	»	—	» »	100.	» »	—	»	13.17 g. glucose.

10 days later 45 g. glucose (6.5 g. per kg.) produces *no glucosuria.*

On the other hand *after 60 g. (8.5 g. per kg.)* it gets *slight glucosuria.* With increasing doses *unlimited capacity of assimilation.* (Table 12.) The nourishment otherwise consisted of 500 g. minced horse-flesh.

Control-test.

Table 13.

Dog of same litter, female, not operated.

13/12:	weight	7.55	kg.	—	Per os	80	g. glucose.	—	Urine:	no glucosuria.
14/12:	»	7.70	»	—	» »	100	» »	—	»	no glucosuria.
15/12:	»	7.75	»	—	» »	120	» »	—	»	no glucosuria.
16/12:	»	7.75	»	—	» »	150	» »	—	Vomiting.	

Nourishment otherwise 500 g. minced horse-flesh.

The control-animal which gets doses rising from 10.6 g. per kg. to 15.50 g. per kg. does not get glucosuria. (Table 13.)

Table 14.

17/1:	weight	10.6	kg.	—	Per os	100	g: glucose	—	Urine:	no glucosuria.
18/1:	»	11.05	»	—	» »	120	» »	—	»	no glucosuria.

After the lapse of one month the tolerance has increased so that doses of up to 120 g. (11 g. per kg.) do not produce glucosuria (Table 14). It was not possible to get the dog to retain larger quantities. The dog grows exceedingly fast and is the largest of its litter. It is lively and strong. Afterwards it receives daily 3 fourths of a litre of skim-milk and 300 g. bread.

Table 15.

$^{13}/_{3}$:	weight	15.00	kg.	—	Per os	750 ccm. skim-milk 300 g. bread	—	Urine:	no glucosuria.
$^{20}/_{3}$:	»	15.45	»	—	» »	80 » glucose	—	»	no glucosuria.
$^{21}/_{3}$:	»	15.60	»	—	» »	100 » »	—	»	0.79 g. glucose.
$^{22}/_{3}$:	»	15.70	»	—	» »	130 » »	—	»	7.95 g. glucose.
$^{23}/_{3}$:	»	15.70	»	—	» »	115 » »	—	»	5.37 g. glucose.

Two months later the tolerance has decreased. The limit for the occurrence of glucosuria is 100 g. glucose, corresponding to 7.44 g. per kg. The dog still shows unlimited capacity of assimilation (Table 15). It does not get glucosuria on the diet it receives daily, consisting of 3-fourths of a litre of skim-milk and 300 g. bread.

In the beginning of April the dog is 9 months old. It is large and strong, weighs about 17 kg. It now gets glucosuria on a diet containing abundance of carbo-hydrates (250 g.), consisting of bread and milk (Table 16).

Table 16.

$^{12}/_{4}$:	weight	16.80	kg.	—	740 ccm. milk 450 g. bread	253 g. carbo-hydr.	—	Urine:	3.05 g. gluc
$^{13}/_{4}$:	»	16.80	»	—	1000 ccm. milk 450 g. bread	260 » »	—	»	12.60 g. gluc.
$^{14}/_{4}$:	»	17.20	»	—	1000 ccm. milk 450 g. bread	260 » »	—	»	38.50 g. gluc.
$^{27}/_{4}$:	»	16.70	»	—	500 » »			»	no glucosuria.
$^{28}/_{4}$:	»	16.55	»	—	500 » »			»	no glucosuria.
$^{29}/_{4}$:	»	16.65	»	—	500 » »			»	no glucosuria.

Under tolerance-test with glucose it does not get glucosuria after 80 g. glucose, but with 100 g. the glucosuria is greater than it was 1 month before. (Table 17.)

Table 17.

$^{21}/_{4}$:	weight	16,80	kg.	—	Per os	80 g. glucose	—	Urine:	no glucosuria.
$^{1}/_{5}$:	»	16.75	»	—	» »	100 » »	—	»	10.95 g. glucose.
$^{3}/_{5}$:	»	16.60	»	—	» »	100 » »	—	»	14.21 g. glucose.
$^{9}/_{5}$:	»	16.95	»	—	» »	100 » »	—	»	12.12 g. glucose.

In the course of 1 month the tolerance again increases. 100 g. glucose produces no glucosuria. (Table 18.)

Table 18.

$^{5}/_{6}$:	weight	16.40	kg.	—	Per	os	100	g.	glucose	—	Urine:	no glucosuria.
$^{14}/_{6}$:	»	16.25	»	—	»	»	100	»	»	—	»	no glucosuria.
$^{27}/_{6}$:	»	16.00	»	—	»	»	100	»	»	—	»	no glucosuria.

Nourishment otherwise 700 g. minced horse-flesh per day.

About the 1st July the dog is 12 months old. It gets glucosuria again after administration of 100 g. glucose:

$^{1}/_{7}$: weight 15.85 kg. — Per os 100 g. glucose — Urine: trace of glucose.

In the course of the month the dog falls off in weight. It suffers from great thirst and passes much urine. In the beginning of August, 1 month after the last test, it gets severe glucosuria on bread and milk:

$^{3}/_{8}$:	weight 12.10 kg. —	400 g. bread 500 ccm. skim-milk	233 g. carbo-hydr.	Urine: 119.97 g. glucose.

The dog was now put on diabetes diet, exclusively protein-fat. Also on this diet it excretes sugar. (Table 19.)

Table 19.

$^{5}/_{8}$:	weight	11.70	kg.	—	500	g.	horse-beef,		30	g.	fat	—	Urine:	50.73 g. glucose.
$^{6}/_{8}$:	»	11.70	»	—	500	»	»	»	30	»	»	—	»	57.12 g. glucose.
$^{7}/_{8}$:	»	11.80	»	—	500	»	»	»	40	»	»	—	»	50.93 g. glucose.
$^{8}/_{8}$:	»	11.75	»	—	500	»	»	»	40	»	»	—	»	55.72 g. glucose.
$^{9}/_{8}$:	»	11.80	»	—	300	»	»	»	70	»	»	—	»	34.56 g. glucose.
$^{0}/_{8}$:	»	11.80	»	—	300	»	»	»	70	»	»	—	»	34.69 g. glucose.

Thus, 10 months after the operation there has arisen spontaneous glucosuria on a diet free from carbo-hydrates.

In the following weeks the dog was utilised for special metabolic experiments.

On the 10th September a new tolerance-test was made with glucose. On the preceding days the dog had daily had a diet consisting of 300 g. horse-beef and 70 g. fat. During this diet the urine contained on an average 34 g. glucose. In addition to this diet the dog got 50 g. and 100 g. glucose.

Table 20.

$^{10}/_{9}$	weight	10.90	kg. —	50 g. glucose,	300 g.	horsebeef,	70 g.	fat —	Urine:	82.60 g. glucose.
$^{11}/_{9}$	»	10.45	» —	100 g. »	300 g.	»	70 g.	» —	»	135.49 g. glucose.

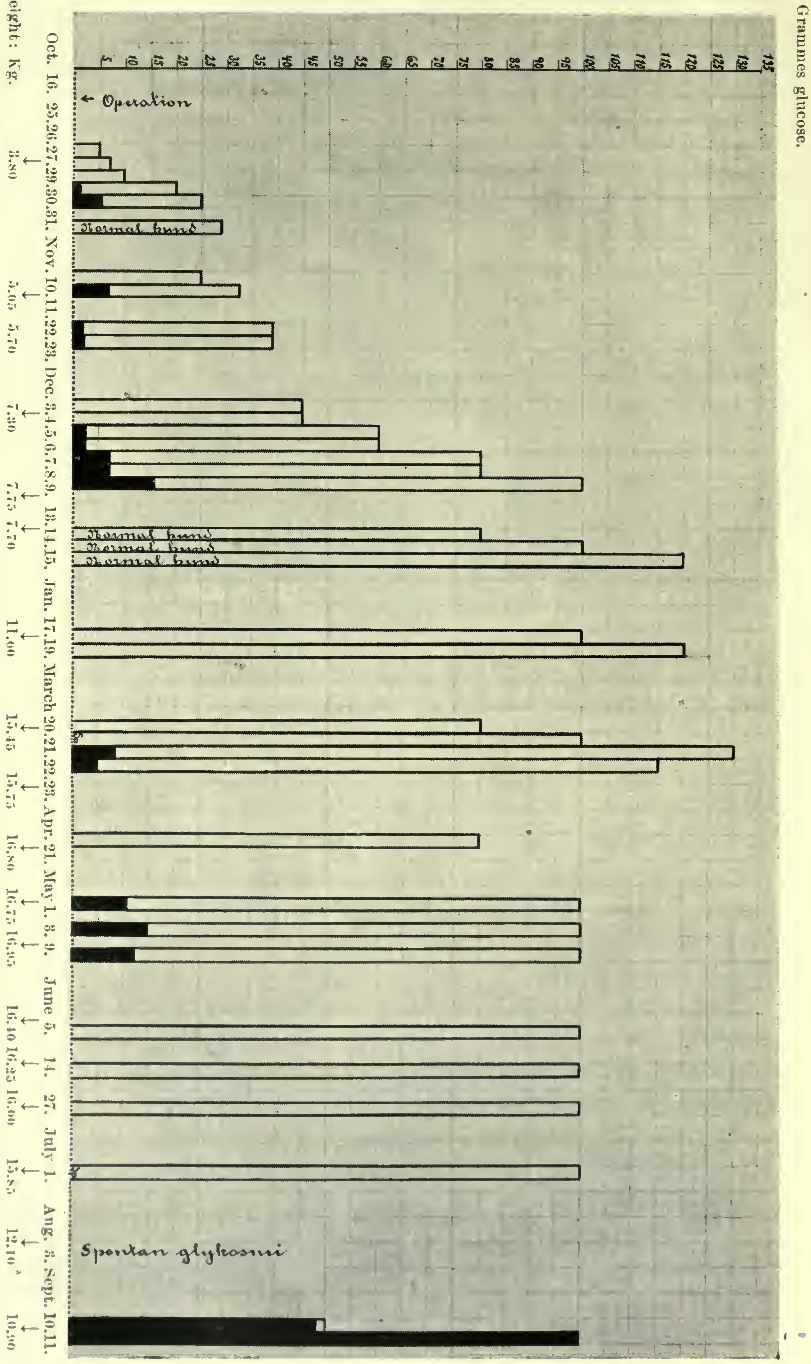

Fig. 2. The whole columns indicate the quantity of glucose given. The dark portions show the amount of glucose excreted in the urine.

The daily protein-fat diet gave a sugar-excretion of 34 g. The dog got in addition the first day 50 g. glucose: excretion 82.6 g.; the second day 100 g. glucose: excretion 135.5 g. (Table 20.) Thus the assimilation-capacity should be: 84—82.6 equal 1.4 g. and 135.5—134 equal 1.5 g. This difference is, however, not so great that it might not be due to fermentation in the intestine. The result of the experiment may therefore be taken to signify that the dog at this point of time has no capacity for assimilation of glucose beyond the quantity of glucose formed from protein that may be assumed to be assimilated, in other words, it discharges all extra sugar and there is now a definite limit of assimilation.

The results of the experiments on this dog may be graphically represented as shown in Fig. 2.

From the above exposition it will be seen that partial extirpation of the pancreas in a dog $3^1/_2$ months old, where 8/9ths of the pancreas have been removed, has occasioned:

Reduced tolerance for glucose after the operation. A continuation of the tolerance-tests showed, however, that the tolerance increased with the growth of the animal. Compared with the tolerance shown by the control-animal, however, the tolerance was still decreased. Two or three months after the operation there intervened an interval of about 6 months' duration, during which the animal was apparently quite normal. During that interval there temporarily occurs a slight decrease in tolerance, glucosuria being produced with 100 g. glucose. After that interval there followed a rapid fall in the tolerance and development of a chronic diabetes.

What is new and most remarkable in these observations is the increasing tolerance. This may be due:

1) Either to the growth of the animal, whereby the number of sugar-consuming cells increases;

2) Or, if we assign to the pancreas a function in connection with the assimilation of sugar, to regeneration, anatomical or functional, of the remnant of the pancreas;

3) Or both to the animal's growth and to regeneration of the remnant of the pancreas.

An investigation with regard to the first point can be made by calculating the quantity of glucose given per kg. of body weight. If the increased tolerance is due *only* to the animal's growth, then the tolerance calculated per kg. of body-weight should be constant. Now, if we reckon out what is the smallest quantity administered per kg. body-weight that is capable of producing glucosuria, it will be seen that the tolerance increases also per kg. of body-weight. This relation can be represented graphically as follows (Fig. 3).

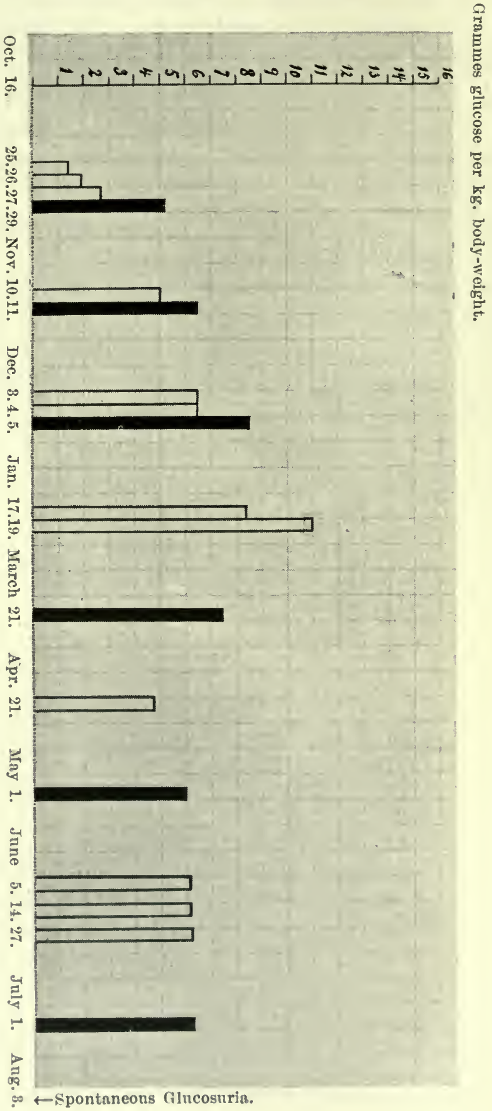

Fig. 3.

The dark columns indicate how much glucose had to be given per kg. body-weight in order to produce glucosuria. The blank columns represent tolerance-tests that did not occasion glucosuria.

There must therefore be also another factor operating here besides the mere increase in the animal's growth.

In order to clear up this point we were tempted, during the interval when the animal was apparently quite normal and glucosuria could not be produced even with the largest doses, to perform an operation to find out whether the remnants of the pancreas had increased in size. We refrained, however, from such an attempt, in the first place for the reason that the operation would present difficulties on account of coalescences, and in the second place because a negative observation with regard to anatomical regeneration would give no enlightenment as to possible hyperfunction of the remnant left behind. On the other hand, an anatomically demonstrable enlargement would, of course, be strong evidence in support of the view that the regeneration that had thus taken place stood in connection with the increased tolerance.

As the dog, on account of this peculiar course which the experiment had taken and with a view to the diabetes which it was assumed would develop, must be regarded as a valuable subject for experiment, it was decided not to risk its life by a new operation, but to leave it to a post-mortem examination later on to clear up this point.

The dog lived for still 8 months after the appearance of the spontaneous glucosuria in August 1917. It could not be again rendered free from sugar even after 2 days' fasting. It was utilised for a number of metabolic experiments, which will be described later on. In the course of that time it steadily lost flesh, and acidosis and acetonuria arose. In January 1918 it weighed 7.60 kg. In the course of February it increased about 1 kg. in weight, probably owing to the fact that it received fat in a more emulsified form and therefore more easily absorbed. It died on the 17th of March 1918 after having taken no nourishment for 4 days. It did not get coma. The cause of death was loss of strength due to failure to take nourishment, which again may be assumed to be due to the intussusception revealed on dissection.

Dog II.

Deerhound, female.

The dogs belongs to the same litter of deerhounds as dog I. It has lived in the laboratory under the same conditions as the latter.

At the time of operation it was *4 months old* and weighed 4.75 kg.

Operation $^8/_{11}$ *1916:* The whole of the vertical portion and the greater part of the horizontal portion were removed. Of the lienal extremity (cauda) there was left behind a piece 3 cm. in size, without connection with the duodenum. Around the blood-vessels on the duodenum there were left behind a couple of small remnants of the pancreas of the size of half a pea. The piece extirpated was 20 cm. long and weighed 14.5 g. The portion left behind was estimated to be 1/8th of the whole gland. (Fig. 4).

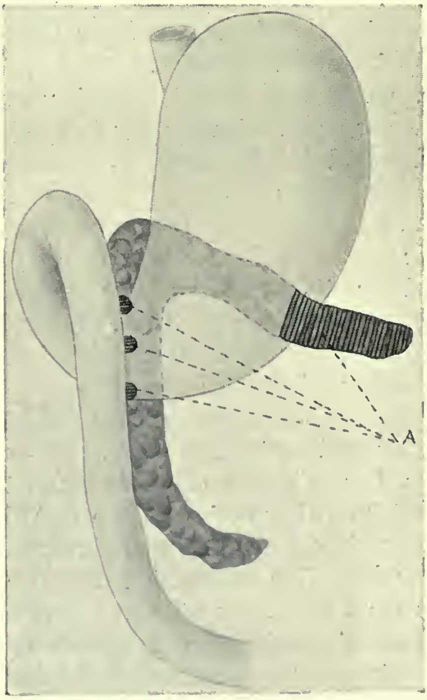

Fig. 4. A — Remnants of pancreas.

The day after the operation the dog got 250 ccm. skim-milk without glucosuria appearing, on the other hand the following day after 500 ccm. skim-milk the urine answers to the reduction-test. It is free from sugar after a diet consisting exclusively of meat, but 1 week after the operation the dog had glucosuria after bread and milk (Table 21):

Table 21.

$^{10}/_{11}$:	weight	4.40	kg.	—	250 ccm. skim-milk	—	Urine:	no glucosuria.
$^{11}/_{11}$:	»	4.35	»	—	500 ccm. » »	—	»	reduces.
$^{12}/_{11}$:	»	4.47	»	—	400 g. horse-beef	—	»	no glucosuria.
$^{17}/_{11}$:	»	4.15	»	—	600 ccm. skim-milk 100 g. bread	—	»	1.26 g. glucose.

The tolerance-test was made 12 days after the operation in the same manner as in the case of the first dog.

Table 22.

$^{22}/_{11}$:	weight	4.10	kg.	—	Per os 28 g. glucose	—	Urine:	2.28 g. glucose.
$^{23}/_{11}$:	»	4.25	»	—	» » 28 g. »	—	»	1.97 g. glucose.

Nourishment otherwise 280 g. minced horse-flesh per day.

The dog gets glucosuria after 28 g. glucose, corresponding to 6.5 g. per kg. body-weight (Table 22).

In the beginning of December the dog got a serious gastroenteritis, which lasted 2 or 3 weeks. The experiment could not be renewed before the middle of January, when the dog had completely recovered and had regained its strength.

Table 23.

$^{17}/_{1}$:	weight	6.0	kg.	—	Per os 60 g. glucose	—	Urine:	1.72 g. glucose.
$^{19}/_{1}$:	»	6.10	»	—	» » 80 g. »	—	»	7.70 g. glucose.

Nourishment otherwise 350 g. minced horse-flesh per day.

The dog gets a slight glucosuria after 60 g. glucose (Table 23). Control-tests were carried out on the non-operated dog and are recorded under the heading: Dog I. No glucosuria.

In the time between the tolerance-tests the dog gets daily 350 g. bread and 750 ccm. skim-milk, which diet does not induce glucosuria.

Table 24.

$^{13}/_{3}$: 350 g. bread, 750 ccm. skim-milk — Urine: no glucosuria.
$^{27}/_{3}$: weight 8.50 kg. — Per os 80 g. glucose — Urine: 0.96 g. glucose.
$^{28}/_{3}$: » 8.45 » — » » 100 g. » — » 6.56 g. glucose.
$^{29}/_{3}$: » 8.50 » — » » 115 g. » — » 9.48 g. glucose.

Nourishment otherwise 500 g. minced horse-flesh daily.

As will be seen, the tolerance is still increasing. 4$^{1}/_{2}$ months after the operation the dog excretes only a trace of sugar after 80 g. glucose. The assimilation-capacity is unlimited (Table 24).

5 months after the operation it still fails to get glucosuria after a diet rich in carbo-hydrates:

$^{13}/_{4}$: 350 g. bread, 750 ccm. skim-milk — Urine: no glucosuria.

It is now, however, on the threshold. A few days later it gets glucosuria after the same diet (Table 25):

Table 25.

$^{5}/_{5}$: 350 g. bread, 790 ccm. skim-milk — Urine: 3.09 g. glubose.
$^{6}/_{5}$: 400 g. » 750 ccm. » » — » 0.72 g. glucose.

On experiment with glucose the tolerance is found to be the same it was a month ago (Table 26).

Table 26.

$^{9}/_{5}$: weight 9.40 kg. — Per os 80 g. glucose — Urine: 1.91 g. glucose.
$^{10}/_{5}$: » 9.30 » — » » 100 g. » — » 3.25 g. glucose.

During the 3 following months, June, July and August, *the weight remains unchanged, but the tolerance increases.*

Table 27.

$^{4}/_{6}$: weight 9.8 kg. 300 g. bread, 700 ccm. skim-milk — Urine: no glucosuria.
$^{5}/_{6}$: » 9.7 » 80 g. glucose, 500 g. minced horse-flesh — Urine: no glucosuria.

The dog does not get glucosuria after the carbo-hydrate-diet of bread and milk, which previously produced glucosuria.

The tolerance-test with 80 g. glucose does not produce glucosuria either (Table 27).

One and a half and two months later it is still free from sugar after respectively 80 g. and 90 g. glucose (Table 28):

Table 28.

$^{20}/_{7}$:	weight 9.80	kg.	—	Per os 80 g.	glucose	—	Urine:	no glucosuria.
$^{2}/_{8}$:	» 9.65	»	—	» » 90 g.	»	—	»	no glucosuria.

Nourishment otherwise in both tests 500 g. minced horseflesh.

The limit is found to lie at 100 g. glucose (Table 29):

Table 29.

$^{24}/_{8}$:	weight 9.65	kg.	—	Per os 100 g.	glucose	—	Urine:	1.50 g. glucose.
$^{27}/_{8}$:	» 9.60	»	—	» » 100 g.	»	—	»	reduces (trace).

Exactly 1 year after the operation the tolerance-limit still lies at 100 g. (Table 30).

Table 30.

$^{8}/_{11}$:	weight 9.80	kg.	—	Per os 100 g.	glucose	—	Urine:	reduces (trace).
$^{22}/_{11}$:	» 9.60	»	—	» » 150 g.	»	—	»	2.17 g. glucose.

The results of the tolerance-tests on this dog have been the same as for dog I: Decreased glucose-tolerance, which however afterwards increases, not proportionally to the animal's weight so that the tolerance per kg. body-weight will be constant, but so that the tolerance calculated per kg. body-weight is augmented.

From $^{1}/_{1}$ 1918, owing to difficulties in obtaining bread and milk, the dog was put on a meat diet. Thereby it increased in weight.

On a tolerance test in April the dog shows a decreased tolerance, although maintaining considerable assimilation-capacity:

$^{14}/_{4}$: weight 12.50 kg. — Per os 100 g. glucose — Urine: 7.00 g. glucose.

The dog's glucose-tolerance is evidently decreasing. We try to determine the limit:

Table 31.

$^{7}/_{5}$:	weight 12.00	kg.	—	Per os 75 g.	glucose	—	Urine:	5.52 g. glucose.
$^{11}/_{5}$:	» 12.20	»	—	» » 50 g.	»	—	»	7.83 g. »
$^{12}/_{5}$:	» 12.30	»	—	» » 25 g.	»	—	»	1.36 g. »
$^{13}/_{5}$:	» 12.35	»	—	» » 20 g.	»	—	»	0.47 g. »
$^{14}/_{5}$:	» 12.40	»	—	» » 15 g.	»	—	»	no glucosuria.
$^{16}/_{5}$:	» 12.70	»	—	» » 20 g.	»	—	»	0.48 g. glucose.

Glucosuria is produced with 20 g. glucose, but not with 15 g. The tolerance is 1.5 g. per kg. (Table 31).

A week later, however, glucosuria is produced also with 15 g. glucose, but not with 10 g. (Table 32):

Table 32.

24/5: weight 12.50 kg. — Per os 15 g. glucose — Urine: 0.29 g. glucose.
25/5: » 12.60 » — » » 10 g. » — » no glucosuria.

The assimilation-capacity was tested by giving 100 g. glucose. This capacity proves also to have decreased since the test of 14th April:

26/5: weight 12.70 kg. — Per os 100 g. glucose — Urine: 16.82 g. glucose.

Starch in quantities of up to 200 g. produce, however, at this point of the time no glucosuria. (Table 33):

Table 33.

29/5: weight 12.70 kg. 200 g. bread + 200 g. minced horse-flesh: no glucosuria.
31/5: » 12.60 » — 400 g. bread: no glucosuria.

(The bread contained 50.70 % starch.)

The tolerance for glucose shows itself to be rapidly decreasing. A week after the last tolerance-test, which did not produce glucosuria with 10 g. glucose, a new test with the same quantity of glucose gives a positive result:

4/6: weight 12.70 kg. — Per os 10 g. glucose — Urine: 0.23 g. glucose.

The tolerance is now less than 1 g. per kg.

The dog now gets glucosuria after 200 g. starch:

6/6: weight 12.70 kg. — 400 g. bread — Urine: reduces (trace of glucose).

At the same time, that the glucose-tolerance lies between 10 and 5 g., the tolerance for starch is very high. (Table 34):

Table 34.

11/6: weight 13.00 kg. — Per os 5 g. glucose — Urine: no glucosuria.
12/6: » 13.00 » — 400 g. bread (200 g. starch) — » 1.22 g. glucose.

The dog is evidently on the point of getting spontaneous glucosuria.

In the course of the last couple of months the glucose-tolerance has been rapidly decreasing. The results of the experi-

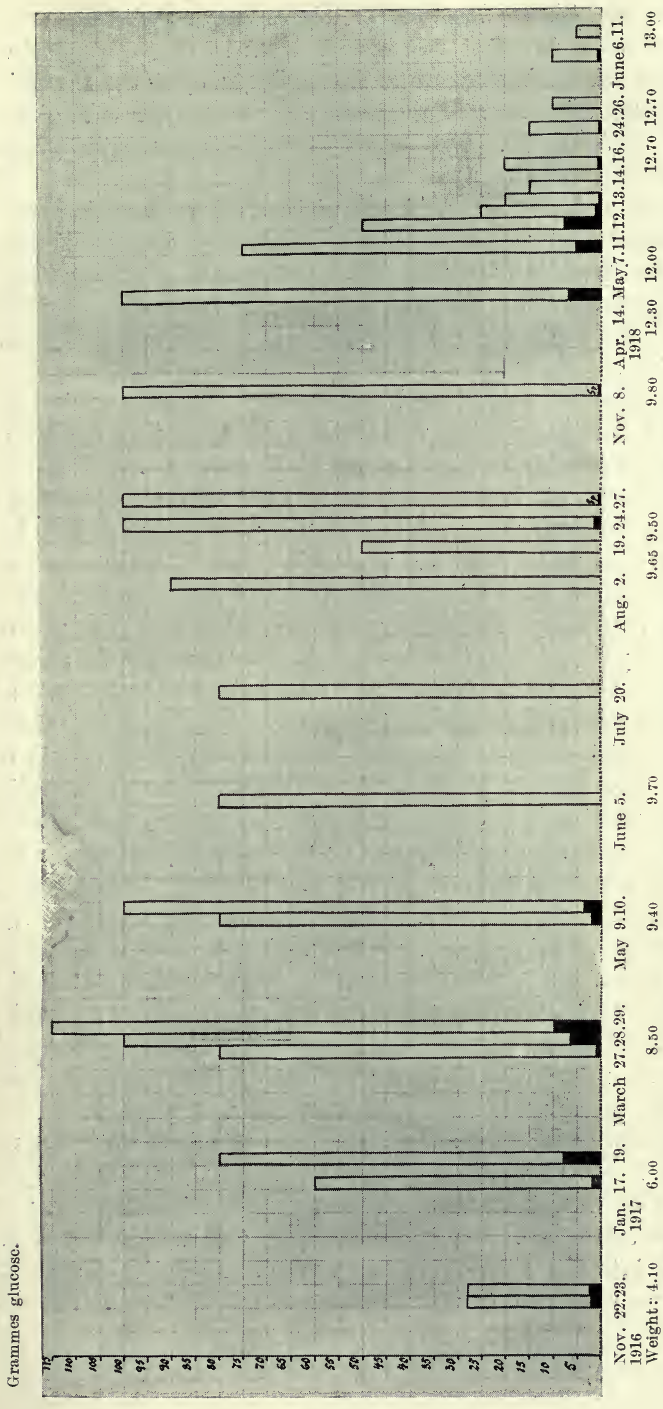

Fig. 5. Graphic representation of the tolerance-tests on dog II. The whole columns indicate the amount of glucose given, the dark columns the quantity of glucose excreted in the urine.

ments have hitherto been completely analogous with the results in the case of the first dog operated on: *A decreased, but nevertheless increasing tolerance immediately after the operation, an interval with normal tolerance and thereafter a rapid decrease of tolerance.* The experiments are represented graphically as before (Fig. 5)

The only difference that the picture of the experiments on these two dogs presents is the duration of the latent stage. From the operation till the appearance of the spontaneous glucosuria or else the decrease of tolerance there elapsed in the case of the first dog 9 months and in the case of the second 19 months.

Investigations regarding blood-sugar were made in the case of this latter dog during the declining stage. The results are recorded in the following chapter on blood-sugar.

At this point it was decided to undertake an operation in order to remove the remnant of the pancreas that had been left. It was to be assumed that this remnant, which was completely severed from the duodenum, must be sclerotised as far as the externally secreting part was concerned. As the dog had not yet got spontaneous glucosuria, it might be assumed that this was prevented by the remnant of the pancreas and that this remnant, in addition to the sclerotic connecting tissue, must consist of the internally secreting elements. This dog should therefore be particularly suited for such an investigation. 19 months had elapsed since the operation, the pancreas-remnant had no excretory duct, the externally secreting cells must be assumed to be degenerated. The dog was apparently quite well, but showed reduced tolerance for glucose. In a short time it might be expected that spontaneous glucosuria would occur. The remaining portion of the pancreas might be supposed to be, functionally regarded, the smallest amount of pancreas that the dog could manage with without getting diabetes. A microscopical examination of the remnant, when removed, ought to show what had prevented glucosuria.

Operation. $^{14}/_{6}$ 1918: Incision from the sternum to the umbilicus, 2 cm. to the left of the scar from the previous operation. The omentum was lifted up without difficulty, there were no adhesions. The milt was large and was easily drawn forward into the opening of the wound. In spite of a careful search no remnants of the pancreas could be found. The duodenum, which was adherent to the lower surface of the liver, was not closely examined.

As the remnant of the pancreas was thus not to be found during the operation, the dog was killed by chloroform and the abdominal organs carefully dissected. The completely sclerotic remnant of the pancreas was found adhering fast to the curvatura major in the neighbourhood of the pylorus on the back of the omentum, surrounded by fat. The microscopical examination of this remnant, *which showed extreme hyperplasia of the Langerhans cell-groups and no trace of externally secreting tissue*, is dealt with together with the whole of the dissection under the heading: post-mortem findings.

Dog III.

Foxterrier, female, 5$^1/_2$ months old. Weight 4.9 kg. Came into the laboratory 6 weeks old. Like the other dogs

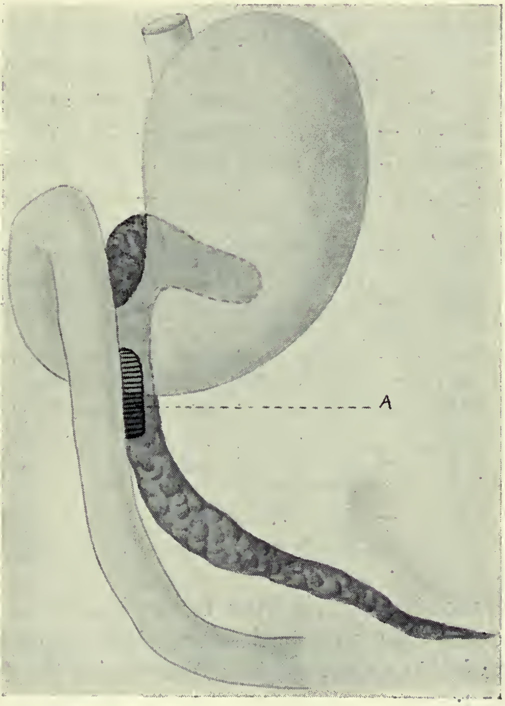

Fig. 6. Dog III. A — Remnant of pancreas.

it has got only bread and milk. Two months before, when the dog was $3^1/_2$ months old and weighed 3.30 kg., a tolerance-test was made on this dog and another dog of the same litter, intended for control- animal, without glucosuria being produced. The experiments have already been described (p. 25).

Operation. $^3/_7$ 1917: The whole of the horizontal portion (which was very short, only 3 cm. long) and the point of the vertical portion were removed. The extirpated pieces were 9.5 cm. long and weighed 7.2 g. The remnant of the pancreas was estimated at 1/7th of the whole gland. (Fig. 6.)

The dog suffered from gastro-enteritis during the first 10 or 12 days after the operation. It lost flesh considerably. After 2 weeks it began to eat again. It got glucosuria after being fed with from half a litre to 1 litre of milk, but became free from sugar when bread was substituted for part of the milk even though the substituted food was richer both in carbo-hydrates and in calories (Table 35):

Table 35.

$^{19}/_{7}$:	weight	3.90	kg.	—	350 g. horse-beef	—	Urine:	no glucosuria.
$^{23}/_{7}$:	»	3.90	»	—	1000 ccm. skim-milk	—	»	7.03 g. glucose.
$^{24}/_{7}$:	»	3.95	»	—	1000 » »	—	»	4.46 g. »
$^{25}/_{7}$:	»	4.05	»	—	500 ccm. skim-milk 70 g. bread	—	»	2.25 g. »
$^{26}/_{7}$:	»	4.00	»	—	500 ccm. skim-milk 70 g. bread	—	»	1.13 g. »
$^{27}/_{7}$:	»	3.95	»	—	500 ccm. skim-milk 70 g. bread	—	»	1.20 g. »
$^{1}/_{8}$:	»	3.80	»	—	250 ccm. skim-milk 150 g. bread	—	»	no glucosuria.
$^{2}/_{8}$:	»	3.85	»	—	250 ccm. skim-milk 150 g. bread	—	»	no glucosuria.
$^{4}/_{8}$:	»	3.85	»	—	250 ccm. skim-milk 250 g. bread	—	»	no glucosuria.
$^{5}/_{8}$:	»	3.95	»	—	250 ccm. skim-milk 250 g. bread	—	»	no glucosuria.

With tolerance-tests made over 1 month after the operation glucosuria cannot be produced even with large quantities of glucose. For lactic sugar, on the other hand, the tolerance is less (Table 36):

Table 36.

$^{8}/_{8}$:	weight	3.80	kg.	—	Per os	10 g.	glucose	—	Urine:	no glucosuria.
$^{9}/_{8}$:	»	3.80	»	—	» »	20 g.	»	—	»	no glucosuria.
$^{10}/_{8}$:	»	3.80	»	—	» »	30 g.	»	—	»	no glucosuria.
$^{13}/_{8}$:	»	3.90	»	—	» »	40 g.	»	—	»	no glucosuria.
$^{14}/_{8}$:	»	3.95	»	—	» »	50 g.	»	—	»	no glucosuria.
$^{15}/_{8}$:	»	3.95	»	—	» »	50 g.	lactic sugar		»	5.67 g. glucose.
$^{16}/_{8}$:	»	4.00	»	—	» »	60 g.	glucose	—	»	no glucosuria.
$^{17}/_{8}$:	»	4.00	»	—	» »	60 g.	lactic sugar		»	5.61 g. glucose.
$^{18}/_{8}$:	»	4.00	»	—	» »	60 g.	glucose	—	»	no glucosuria.
$^{19}/_{8}$:	»	4.10	»	—	» »	70 g.	»	—	»	no glucosuria.
$^{20}/_{8}$:	»	4.15	»	—	» »	70 g.	lactic sugar		»	6.41 g. glucose.
$^{21}/_{8}$:	»	4.25	»	—	» »	80 g.	glucose	—	»	no glucosuria.
$^{22}/_{8}$:	»	4.25	»	—	» »	80 g.	lactic sugar		»	8.51 g. glucose.
$^{23}/_{8}$:	»	4.30	»	—	» »	90 g.	glucose	—	»	no glucosuria.
$^{24}/_{8}$:	»	4.35	»	—	» »	100 g.	»	—	»	no glucosuria.

The dog tolerates up to 25 g. glucose per kg. body-weight without getting glucosuria. The attempt to give still larger doses caused vomiting.

2 months after the foregoing tests glucosuria was produced for the first time in this dog with 100 g. glucose.

$^{25}/_{10}$: weight 5.80 kg. — Per os 100 g. glucose — Urine: reduces (trace).

Up to the end of December 1917 the dog got food consisting of bread and milk. From January 1918 exclusively minced horse-flesh. The dog thrives, is exceedingly lively, apparently quite well.

A tolerance-test in May with 100 g. glucose gives a positive result with a glucosuria of 2.49 g. On the other hand, it remains free from sugar after 75 g. glucose (Table 37):

Table 37.

$^{27}/_{5}$-1918:	weight	7.70	kg.	—	Per os	100 g.	glucose	—	Urine:	2.49 g. glucose.
$^{28}/_{5}$ »	»	7.75	»	—	» »	75 g.	»	—	»	free from sugar.

The tolerance at this point of time is 12.6 g. per kg.

The dog increases rapidly in weight. It gets fat. It is lively and buoyant. In the course of 1 month it gains over 1 kg. in weight:

$^{28}/_{5}$: weight 7.75 kg.
$^{8}/_{6}$: » 8.10 »
$^{20}/_{6}$: » 8.35 »
$^{1}/_{7}$: » 8.50 »
$^{9}/_{7}$: » 8.80 »

The dog is $1^{1}/_{2}$ years old and long since full-grown. The increase in weight is therefore not due to the animal's growth.

6 weeks after the foregoing experiment new tolerance-tests are made. It is then seen that the tolerance has decreased (Table 38):

Table 38.

$^{11}/_{7}$:	weight 8.80 kg.	—	Per os 100 g. glucose	—	Urine: 3.37 g. glucose.
$^{12}/_{7}$:	» 8.85 »	—	» » 75 g. »	—	» 1.24 g. »
$^{13}/_{7}$:	» 8.80 »	—	» » 60 g. »	—	» 0.45 g. »
$^{15}/_{7}$:	» 8.90 »	—	» » 50 g. »	—	» trace.
$^{16}/_{7}$:	» 8.80 »	—	» » 40 g. »	—	» free from sugar.

The limit for the occurrence of glucosuria lies at 50 g. glucose, equal to 5.6 g. per kg. The assimilation-capacity is unlimited.

One year has now elapsed since the operation. In the course of the last month the glucose-tolerance has rapidly decreased. The dog is obviously in stadium decrementi and on the point of developing spontaneous glucosuria. Just like the two previous dogs it has during this period increased in weight and become fat.

Otherwise the experiments with this dog present a somewhat divergent picture from those with the other dogs. *It shows a high tolerance for glucose after an operation leaving behind not more pancreas-tissue than 1/7th of the whole gland.* It shows, however, a decreased tolerance for carbo-hydrates on a diet of bread and milk, and in tolerance-tests with lactic-sugar alone the glucosuria is easily produced with comparatively small quantities. *Not until 1 year after the operation does the dog show a decreased tolerance for glucose, a tolerance which, as in the case of the other dogs, rapidly diminishes.*

In Fig. 7 the experiments on this dog are presented graphically together with the control-tests.

In considering what can be the reason why this dog, in contrast to the other operated dogs, shows so high a tolerance for

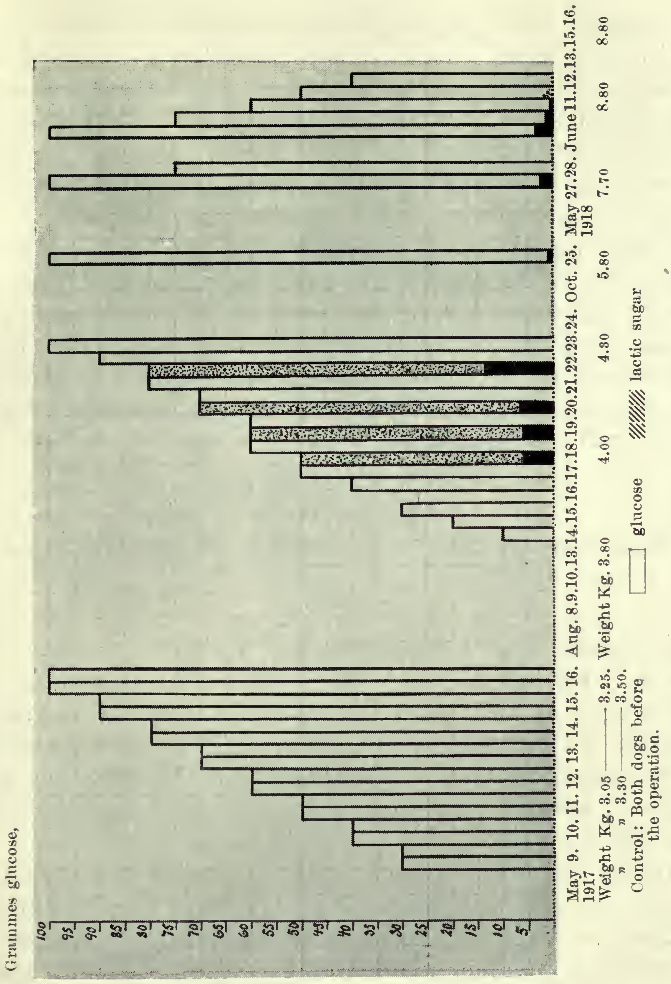

Fig. 7.

glucose immediately after the operation, we must have regard to the following points:

The remnant of the pancreas left behind was estimated at 1/7th of the whole gland, in the case of the other dogs at 1/9th and 1/8th only. In the next place the dog is small and of a different breed. Finally, we must have regard to the possibility of aberrant gland-tissue. That the explanation would turn out to lie in the presence of such tissue was not altogether improbable, the more so as the pancreas showed itself during the operation to be of a different appearance, different shape and situation than usual. If such tissue was not found the explanation would have to be sought for in the above-mentioned circumstances, and especially in the size of the pancreas-remnant in proportion to the whole gland. 1/7th of the pancreas, so long as it was capable of functioning, would then be sufficient to maintain a normal tolerance for glucose.

The dog was killed 1 year after the operation (16/7-1918). The remnant of the pancreas was found as a hard lump on the duodenum, adhering fast to the lower surface of the liver. The abdominal organs were carefully dissected without any trace of pancreas-tissue being found. The microscopical examination of the remnant and the other findings made in dissection will be dealt with later on.

2. Tolerance-test after operation on full-grown animals.

Dog IV.

Deerhound, female, 9 months old. Weight 13,75 kg.

The dog belongs to the litter of deerhounds that came to the laboratory 6 weeks old. It has lived the whole time since exclusively on bread and milk. At the time of the operation it is 9 months old and weighs 13,75 kg. The operation was exactly the same as that performed on the first operated male dog of the same litter.

Operation $^{18}/_{4}$ *1917:* The whole of the horizontal portion and the point of the vertical portion were removed. The pieces extirpated were 18 cm. long and weighed 18,5 g. The piece left behind lay around the ductus pancreaticus, it was 2 cm. long and was estimated to be 1/9th of the whole gland. (Fig. 8.)

Immediately after the operation glucosuria appeared on feeding with carbo-hydrates (Table 39):

Table 39.

$^{21}/_{4}$	weight	12,50	kg.	—	500 ccm.	skim-milk	—	Urine:	11,84 g.	glucose.
$^{22}/_{4}$	›	12,50	›	—	1,000 ccm.	›	—	›	34,80 g.	›
$^{23}/_{4}$	›	12,75	›	—	1,000 ccm.	›	—	›	34,80 g.	›
$^{24}/_{4}$	›	12,25	›	—	only water		—	›	no glucosuria.	

26/4 weight 12,55 kg — 100 g. dog-biscuits — Urine: 35,20 g. glucose.
(60 g. carbo-hydrates)
27/4 » 11,90 » — 60 g. dog-biscuits — » 24,50 g. glucose.
(36 g. carbo-hydrates)

14 days after the operation the first tolerance-tests were made with glucose.

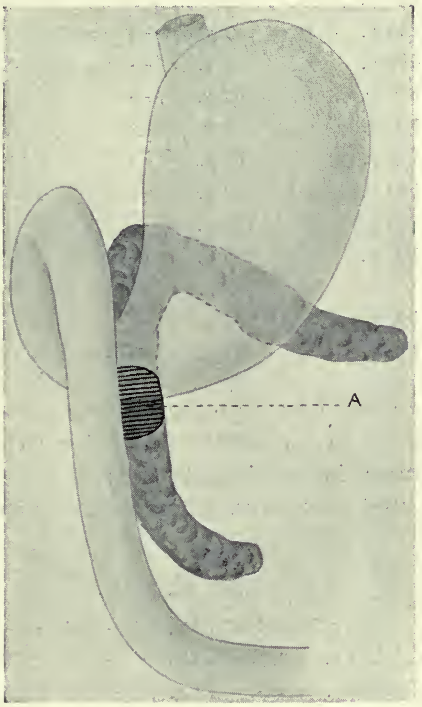

Fig. 8. Dog No. IV. A — Remnant of pancreas.

Table 40.

1/5 weight 11,50 kg. — Per os 50 g. glucose — Urine: 48,90 g. glucose.
2/5 » 11,35 » — » » 50 g. » — » 32,90 g. »

The dog got otherwise: the first day 400 g minced horse-flesh (500—100 g.). The second day: 100 g. minced horse-flesh (500 g.—400 g.).

The dog shows some assimilation-capacity for glucose (Table 40).

One month after the operation there is a considerable glucosuria after protein-fat (horse-beef, emulsified fat). On diminishing the amount of meat the dog became free from sugar (Table 41):

Table 41.

10/5	food:	600 g.	horse-beef		Urine:	34,13 g.	glucose
22/5	»	600 g.	»		»	45,27 g.	»
27/5	»	400 g.	»	60 g. fat —	»	39,00 g.	»
28/5	»	400 g.	»	60 g. » —	»	41,32 g.	»
29/5	»	200 g.	»	60 g. » —	»	21,20 g.	»
31/5	»	100 g.	»	70 g. » —	»	4,66 g.	»
1/6	»	100 g.	»	70 g. » —	»	6,14 g.	»
2/6	»	100 g.	»	70 g. » —	»	2,22 g.	»
3/6	»	100 g.	»	100 g. » —	»	no glucosuria.	
4/6	»	100 g.	»	130 g. » —	»	no glucosuria.	
5/6	»			130 g. » —	»	no glucosuria.	
6/6	»	100 g.	»	70 g. » —	»	no glucosuria.	
7/6	»	100 g.	»	70 g. » —	»	no glucosuria.	

After the dog has been free from sugar for a week a tolerance-test is made in immediate succession to this sugar-free period. The sugar is administered as a supplement to the food given in the last days, which had not produced glucosuria:

Table 42.

8/6		100 g.	horse-beef	70 g. fat —	Urine:	no glucosuria.	
9/6	20 g. glucose	100 g.	»	70 g. » —	»	7,95 g.	glucose.
10/6	20 g. »	100 g.	»	70 g. » —	»	7,69 g.	»
11/6	20 g. »	100 g.	»	70 g. » —	»	8,61 g.	»
12/6	20 g. »	100 g.	»	70 g. » —	»	12,31 g.	»
13/6	20 g. »	100 g.	»	70 g. » —	»	13,97 g.	»
14/6		100 g.	»	70 g. » —	»	no glucosuria.	

The dog shows itself to be capable of assimilating about 10 g. glucose.

The assimilation-capacity diminishes with steadily continued administration of glucose. On leaving out the glucose and reverting to the previous diet the dog at once becomes again free from sugar. (Table 42.)

After these experiments the dog is taken out of the metabolic cage. It gets a diet consisting of 100 g horse-beef and 70 g fat.

On examination 14 days later it is found to be still free from sugar on this diet. A tolerance-test is now made with boiled starch in addition to the above diet:

Table 43.

$^{30}/_{6}$	food:	100 g. horse-beef	70 g. fat	Urine:	no glucosuria.
$^{1}/_{7}$	›	100 g. ›	70 g. ›	›	no glucosuria.
$^{2}/_{7}$	›	20 g. boiled starch	100 g. horse-beef 70 g. fat	›	no glucosuria.
$^{3}/_{7}$	›	20 g. › ›	100 g. horse-beef 70 g. fat	›	no glucosuria.
$^{4}/_{7}$	›	100 g. horse-beef	70 g. fat	›	no glucosuria.

20 g. boiled starch does not produce glucosuria (Table 43). The excrements did not give starch-reaction.

Table 44.

$^{9}/_{7}$	20 g. glucose —	100 g. horse-beef —	70 g. fat —	Urine: 2,97 g. glucose
$^{10}/_{7}$	20 g. › —	100 g. › —	70 g. › —	› 3,15 g. ›
$^{11}/_{7}$		100 g. › —	70 g. › —	› no glucosuria.

The assimilation-capacity for glucose has increased since the last test four weeks ago (Table 44).

On increasing the quantity of protein the dog again gets glucosuria, even though this increase is effected by replacing the fat with meat having the same caloric value (Table 45).

Table 45.

$^{12}/_{7}$	100 g. horse-beef —	70 g. fat —	Urine: no glucosuria.
$^{13}/_{7}$	200 g. › —	60 g. › —	› no glucosuria.
$^{14}/_{7}$	200 g. › —	60 g. › —	› no glucosuria.
$^{16}/_{7}$	300 g. › —	50 g. › —	› 6,47 g. glucose.
$^{17}/_{7}$	300 g. › —	50 g. › —	› 6,88 g. ›
$^{21}/_{7}$	400 g. › —	40 g. › —	› 13,34 g. ›
$^{22}/_{7}$	400 g. › —	40 g. › —	› 13,50 g. ›

Two months later the dog is no longer, as it was before, free from sugar after 100 g. horse-flesh (Table 46):

Table 46.

$^{8}/_{9}$	weight 10,00 kg.	100 g. horse-beef —	100 g. fat —	Urine: 9,35 g. glucose.
$^{9}/_{9}$	› 10,00 kg.	100 g. › —	100 g. › —	› 8,99 g. ›

After 1 day's fasting, followed by a diet consisting exclusively of fat, it becomes, however, free from sugar. But it at once gets glucosuria when meat is added (Table 47):

Table 47.

14/9 Fasting day	Urine:	no glucosuria.
15/9 110 g. fat	›	no glucosuria.
16/9 150 g. ›	›	no glucosuria.
18/9 100 g. horse-flesh — 100 g. fat —	›	6,28 g. glucose.

The dog was now utilised, like dog I, for a number of special experiments. There gradually developed severe acidosis and acetonuria, while at the same time the dog lost flesh. It died on the 31st May 1918 (duration of illness 13 months).

Thus, in the case of this dog, which was operated on when full-grown, the glucosuria appeared immediately after the operation, when it was on a diet rich in carbo-hydrates.

In concluding this chapter on glucose-tolerance after partial extirpation of the pancreas it will be convenient to sum up the observations made. These are briefly as follows:

1. Of 4 dogs belonging to the same litter 3 were operated on (Dog I, II & IV), the fourth was used as control-animal. Of the 3 operated dogs 2 were operated when puppies (I & II), the third when full-grown (IV). From the young animals (I & II) there were removed respectively 8/9ths and 7/8ths of the pancreas. In the first months after the operation these dogs showed a reduced glucose-tolerance as compared with the control-animal. The tolerance, meanwhile, gradually increases as the animals grow up, both absolutely and relatively in proportion to the weight of the dogs. With dog I this period lasts about 3 months, with dog II about 8 months. After an interval of 6 and 8 months respectively with apparently normal tolerance these dogs which were operated when puppies again show a decreased tolerance, and in one of them (Dog I) there develops a regular diabetes. The other (Dog II) was killed at this point for purposes of examination. From the full-grown dog (IV) there were removed 8/9ths of the pancreas. This dog shows, however, no increasing tolerance and has no stage of freedom from sugar, but gets spontaneous glucosuria with chronic progress immediately after the operation.

2. Of 2 dogs belonging to the same litter (terriers) one (Dog III) was operated, the other was for control. After removal of 6/7ths of the pancreas it shows no decreased tolerance for glucose in the first 10 months after the operation. It tolerates up to 100 g glucose (23 g glucose per kg body-weight) without getting glucosuria. 10 months after the operation it gets glucosuria after administration of glucose, whereafter the tolerance further diminishes during the following 2 months.

The considerations of a general and special nature which these results give occasion to will be dealt with later on.

Blood-sugar.

The earlier investigations regarding the concentration of blood-sugar in the dog led to results that are far from reconcilable. The following are quoted by BANG [(37) p. 31]; OTTO (1885) found from 0,13 % to 0,21 %, average 0,16 %; SEEGEN (1884) 0,11 % to 0,23 %, average 0,14 %; ABDERHALDEN (1898) 0,07 % to 0,11 %; MICHAELIS and ROMA (1909) 0,10 % to 0,22 % (by polarisation), average 0,17 %; DE MEYER (1910) 0,04 % to 0,19 % (after BERTRAND), average 0,10 %; TAKAHASHI 0,08 % to 0,19 %, average 0,12 % (by polarisation, partly also by reduction after BERTRAND, DAVY and BANG); RINDERSPACHER (1910) 0,09 % to 0,12 %, average 0,10 %; ROTH (1912) 0,09 % to 0,12 %

BANG sees in these divergent results a proof that the dog is little suited for investigations regarding hyperglycemia. The degree of physiological variation is too great to allow us with certainty to draw conclusions from the experimental operations. He does not, however, exclude the possibility that the analyses recorded may show incorrect values, and he regards continued investigations regarding the blood-sugar in the dog as desirable. With BANG's Micromethod (38) I have carried out such investigations, which shall be recorded here.

1. Concentration of blood-sugar in normal dogs and in operated, non-diabetic dogs.

Normal Dogs.

All the animals examined were at the time of examination accustomed to the laboratory and did not suffer the slightest disturbance from the treatment. The dogs were fasting when examined. 24 hours had elapsed since the last feed. The blood was taken from a vein in the ear. The amount of blood-sugar was determined by Bang's method (38).

Table 48.

Dog No.	Date	n/200 ccm. iodine	Quantity of blood	Sugar %
VI	$^{4}/_{6}$	0,56	116 mg.	0,088
›	›	0,46	100	0,085
›	$^{6}/_{6}$	0,48	96	0,093
›	›	0,40	76	0,092
III	$^{5}/_{11}$	0,60	137	0,087
›	›	0,56	123	0,090
›	›	0,58	127	0,090
›	›	0,60	136	0,088
VII	$^{20}/_{11}$	0,66	141	0,095
›	›	0,48	95	0,094

Average concentration of blood-sugar in 10 tests: 0,892 %.

Operated, non-diabetic Dogs.

Technics as before.

Table 49.

Dog No.	Date	n/200 ccm. iodine	Quantity of blood	Sugar %
II	$^{4}/_{11}$	0,56	129 mg.	0,085
›	›	0,48	113	0,080
›	›	0,56	128	0,085
›	›	0,56	138	0,080
›	›	0,52	121	0,082
›	›	0,54	122	0,086
›	›	0,54	126	0,083
›	$^{6}/_{11}$	0,58	139	0,082
›	›	0,60	140	0,085
›	$^{7}/_{11}$	0,58	139	0,082
›	›	0,56	126	0,087

Dog No.	Date	n/200 ccm. iodine	Quantity of blood	Sugar %
II	$^{22}/_{11}$	0,68	144 mg.	0,097
»	$^{10}/_{5}$	0,52	107	0,093
»	»	0,48	96	0,093
»	$^{11}/_{5}$	0,52	124	0,080
»	»	0,60	143	0,083
»	$^{12}/_{5}$	0,60	140	0,086
»	»	0,46	90	0,090
»	$^{13}/_{5}$	0,56	123	0,090
»	»	0,52	119	0,084
»	$^{15}/_{5}$	0,56	115	0,087
»	»	0,60	124	0,096
»	$^{16}/_{5}$	0,58	146	0,080
»	»	0,52	119	0,083
»	»	0,52	118	0,085
»	»	0,56	125	0,088
»	$^{23}/_{5}$	0,54	112	0,088
»	»	0,62	127	0,090
»	$^{24}/_{5}$	0,60	139	0,087
»	»	0,56	116	0,088
»	$^{25}/_{5}$	0,46	100	0,085
»	»	0,54	130	0,081
»	$^{27}/_{5}$	0,58	124	0,092
»	»	0,62	140	0,086

As will be seen from Tables 48 and 49 there is no difference in the concentration of blood-sugar in normal dogs and in partially depancreatised, non-diabetic dogs in a fasting condition. The values lie about 0,08 % and 0,09 %.

In the following chapter there will be described a number of experiments made in order to investigate the relation between glycemia and glucosuria after tolerance-tests on normal and on operated animals with and without diabetes.

2. Relationship between glycemia and glucosuria.

Amongst human beings the relationship between glycemia and glucosuria has been investigated by Jacobsen (39). When the blood-sugar under alimentary tolerance-tests on normal individuals rose to over 0,18 %, glucosuria nearly always occurred, when it rose to 0,15 % glucosuria hardly ever occurred. With the intermediate values some got glucosuria, others did not.

Jacobsen observed a similar relationship between glycemia and glucosuria in diabetes. Patients with renal diabetes formed an exception, as these latter could get glucosuria with a concentration of blood-sugar lying between 0,15 and 0,12 %.

Hamman and Hirschman (40) have found on investigation of 50 cases that, if the blood-sugar did not exceed 0,17 %, the urine was free from sugar, but if it reached 0,18 % or more, glucosuria occurred.

There are no records of similar experiments on dogs.

a. Hyperglycemia without glucosuria in normal animals.

The investigations regarding blood-sugar were carried out by means of tolerance-tests made according to the methods already described. The glucose was administered by means of the stomach-tube in a 20 % solution on an empty stomach, 24 hours after the last feeding. The dogs utilised were at the time of the experiments accustomed to the laboratory. They were not in the least disturbed by the introduction of the stomach-tube and maintained altogether an immovable indifference both during this operation and during all other treatment. The blood was taken from a vein in the ear.

Dog VI.

Test on 4th June — 100 g. glucose.

Table 50.

Blood-sugar, per cent.						
Before the test	After 100 g. glucose in 500 ccm. water.					
	½ hour later	1 hour later	1½ hours later	2 hours later	2½ hours later	3 hours later
0,09	0,15	0,17	0,16	0,14	0,12	0,11

Urine free from sugar.

The glycemia is at the highest, 0,17, after the lapse of 1 hour. No glucosuria appears. (Table 50 and Fig. 9.)

Test on 6th June — *100 g. glucose.*

Table 51.

Blood-sugar, per cent.								
Before the test	After 100 g. glucose in 500 ccm. water.							
	$^1/_2$ hour later	1 hour later	$1^1/_2$ hours later	2 hours later	$2^1/_2$ hours later	3 hours later	$3^1/_2$ hours later	4 hours later
0,08	0,10	0,11	0,12	0,12	0,13	0,13	0,12	0,11

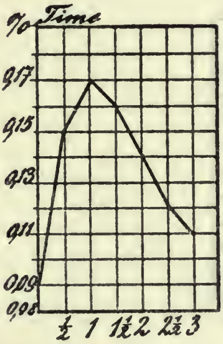

Fig. 9.
Test $^4/_6$ — 100 g. glucose.
Urine free from sugar.

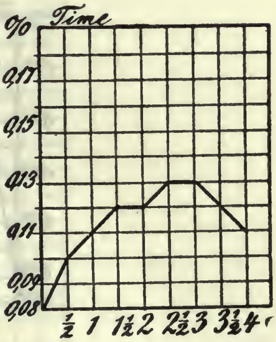

Fig. 10.
Test $^6/_6$ — 100 g. glocose.
Urine free from sugar.

The urine passed 4 hours after the beginning of the test (270 ccm.) was free from sugar. The percentage of blood-sugar does not rise so suddenly as in the previous test, and it does not go higher than 0,13 %. The highest percentage is reached after $2^1/_2$ hours, which indicates that the absorption in this case has taken place more slowly. (Table 51 and Fig. 10.)

Dog V.

Test $^5/_{11}$ — *100 g. glucose.*

Table 52.

Blood-sugar, per cent.						
Before the test	After 100 g. glucose in 500 ccm. water.					
	½ hour later	1 hour later	1½ hours later	2 hours later	2½ hours later	3 hours later
0,09	0,14	0,16	0,15	0,14	0,13	0,10

Urine free from sugar. Greatest concentration of blood-sugar 0,16 %. (Table 52 and Fig. 11.)

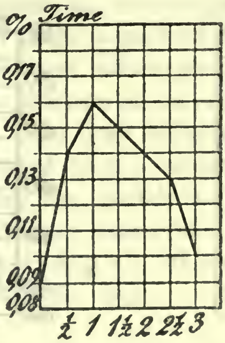

Fig. 11. Test $^5/_{11}$ — 100 g. glucose.
Urine free from sugar.

The concentration of blood-sugar was not greater than 0,17 % in either of these dogs, neither of which got glucosuria after 100 g. glucose.

The highest percentage is reached in the course of 1 hour, after which it again sinks somewhat more slowly till it reaches the normal in the course of a couple of hours. Where the rise is less sudden, the glycemia does not reach so great a height either, but on the other hand it is of longer duration.

b. Hyperglycemia with glucosuria in normal animals.

Dog VII.

Test $^{20}/_{11}$ — *100 g. glucose.*

Table 53.

Blood-sugar, per cent.					
Before the test	After 100 g. glucose in 500 ccm. water.				
	½ hour later	1 hour later	1½ hours later	2½ hours later	3 hours later
0,09	0,13	0,16	0,21	0,18	0,16

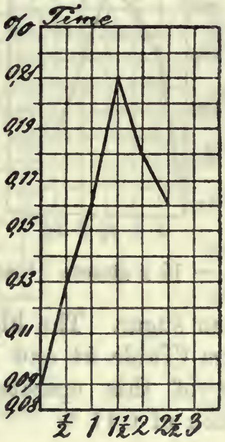

Fig. 12. Test $^{20}/_{11}$ — 100 g. glucose.
Urine reduces.

Urine reduces, phenylhydrazin-test positive.

Polarimeter 0, titration after Bang 0,15 %, equal to 0,82 g. glucose.

In this dog, which gets glucosuria after 100 g. glucose, the blood-sugar percentage rises to 0,21 %. The maximum is reached after 1½ hours. (Table 53 and Fig 12.)

c. Hyperglycemia without glucosuria in depancreatised dogs.

Dog II, partially depancreatised, non-diabetic.

Test $^{13}/_{5}$ — *15 g glucose.*

Table 54.

Blood-sugar, per cent.					
Before the test	After 15 g. glucose in 75 ccm. water.				
	½ hour later	1 hour later	1½ hours later	2 hours later	2½ hours later
0,08	0,14	0,16	0,17	0,14	0,11

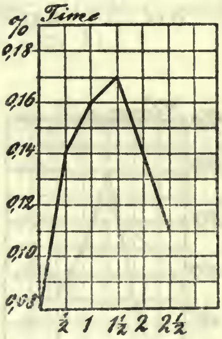

Fig. 13. Test $^{13}/_{5}$ — 15 g glucose. Urine free from sugar.

The urine contains no sugar. The highest percentage, 0,17, is reached in 1½ hours (Table 54 and Fig. 13). No sugar is excreted in the urine of this operated dog either with a blood-sugar concentration of 0,17 %.

Test $^{24}/_{5}$ — *10 g. glucose.*

Table 55.

Blood-sugar, per cent.				
Before the test	After 10 g. glucose in 50 ccm. water.			
	½ hour later	1 hour later	1½ hours later	2 hours later
0,08	0,14	0,16	0,15	0,10

Urine free from sugar. Greatest concentration of blood-sugar 0,16 %. (Table 55 and Fig. 14.)

Test $^{10}/_{6}$ — *5 g. glucose.*

Table 56.

Blood-sugar, per cent.			
Before the test	After 5 g. glucose in 25 ccm. water.		
	$^{1}/_{2}$ hour later	1 hour later	$1^{1}/_{2}$ hours later
0,08	0,11	0,10	0,08

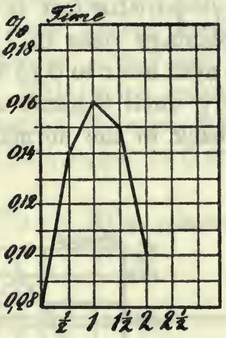

Fig 14.
Test $^{24}/_{5}$ — 10 g. glucose.
Urine free from sugar.

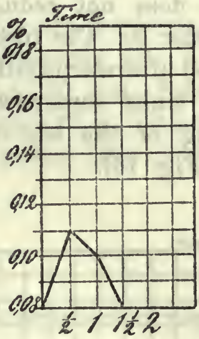

Fig. 15.
Test $^{10}/_{6}$ — 5 g. glucose.
Urine free from sugar.

In this dog there is a perceptible increase in the percentage of blood-sugar even after quite small quantities of glucose. (Table 56 and Fig. 15.)

The experiments have shown that glucosuria does not occur so long as the concentration of blood-sugar does not exceed 0,17 %.

d. Hyperglycemia with slight glucosuria in depancreatised animals.

Dog III, partially depancreatised, non-diabetic.
Test $^{24}/_{10}$ — *100 g. glucose.*

Table 57.

Blood-sugar, per cent.						
Before the test	After 100 g. glucose in 500 ccm. water.					
	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later	6 hours later
0.09	0.19	0.15	0.14	0.12	0.10	0.09

Urine does not reduce, *but phenylhydrazin-test is positive.* Polarimeter 0. The blood-sugar percentage rises in 1 hour to *0.19 %* and afterwards falls during the next hour to 0.15 %, whereafter it sinks somewhat more slowly until 6 hours after the beginning of the test it has come back to the normal (Table 57 and Fig. 16).

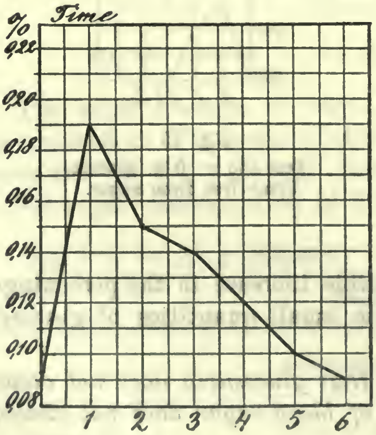

Fig. 16. Test $^{24}/_{11}$ — 100 g. glucose. Trace of sugar in urine.

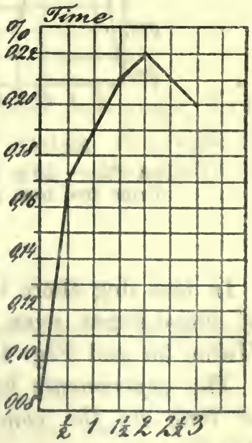

Fig. 17. Test $^{7}/_{10}$ — 100 g. glucose. 0.23 g. sugar in urine.

Dog II.

Test $^7/_{10}$ — *100 g. glucose.*

Table 58.

Blood-sugar, per cent.								
Before the test	After 100 g. glucose in 500 ccm. water.							
	5 min. later	15 min. later	30 min. later	45 min. later	1 hour later	$1^1/_2$ hours later	2 hours later	3 hours later
0.08	0.11	0.17	0.17	0.18	0.19	0.21	0.22	0.20

Greatest concentration of blood-sugar 0.22 %. Urine contains sugar. (Table 58 and Fig. 17.)

Urine was passed immediately before the beginning of the test. Likewise, urine was passed spontaneously after $3^1/_2$ hours exactly. This urine reduces. Quantity 250 ccm. Polarimetric determination of sugar 0.094 %, equal to 0.23 g. Titration after Bang 0.11 %, equal to 0.27 g. Urine passed later is free from sugar.

Test $^{12}/_5$ — *20 g. glucose.*

Table 59.

Blood-sugar, per cent.					
Before the test	After 20 g. glucose in 100 ccm. water.				
	$^1/_2$ hour later	1 hour later	$1^1/_2$ hours later	2 hours later	$2^1/_2$ hours later
0.09	0.20	0.20	0.15	0.10	0.10

The urine, passed 2 hours after the beginning of the test (125 ccm.), reduces. Polarimetric 0.47 g. glucose. Passed later 610 ccm., free from sugar. Greatest concentration of blood-sugar 0.20 % (Table 59 and Fig. 18).

Test $^{15}/_5$ — *20 g. glucose.*

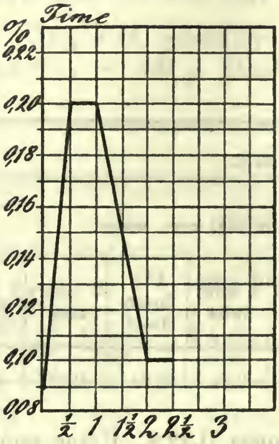

Fig. 18. Test $^{12}/_5$ — 20 g. glucose. 0.47 g. sugar in urine.

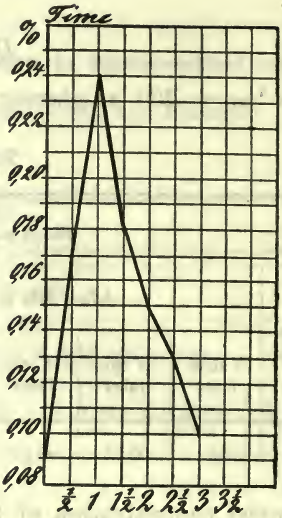

Fig. 19. Test $^{15}/_5$ — 20 g. glucose. 0.48 g. sugar in urine.

Table 60.

Blood-sugar, per cent.						
Before the test	After 20 g. glucose in 100 ccm. water.					
	½ hour later	1 hour later	1½ hours later	2 hours later	2½ hours later	3 hours later
0.09	0.17	0.24	0.18	0.15	0.13	0.10

1 hour after the beginning of the test the concentration of blood-sugar is 0.24 % (Table 60). 3 hours after beginning passed 210 ccm. urine, which reduces. Polarimetric 0.48 g. glucose. Passed later 490 ccm. urine, free from sugar. *In this test the rise is considerable but of quite short duration, which is probably the reason why the glucosuria is not greater. The curve is pointed (Fig. 19). The percentage of blood-sugar remains only a short time at the height at which glucosuria is produced. In a subsequent test on the same dog* ($^{22}/_{11}$, *p.* 64) *the glucosuria is greater, although the hyperglycemia is less.*

Test $^{23}/_5$ — *15 g. glucose.*

Table 61.

Blood-sugar, per cent.					
Before the test	After 15 g. glucose in 75 ccm. water.				
	½ hour later	1 hour later	1½ hours later	2 hours later	2½ hours later
0.09	0.16	0.22	0.21	0.19	0.15

Greatest concentration of blood-sugar 0.22 %. (Table 61, Fig. 20.)

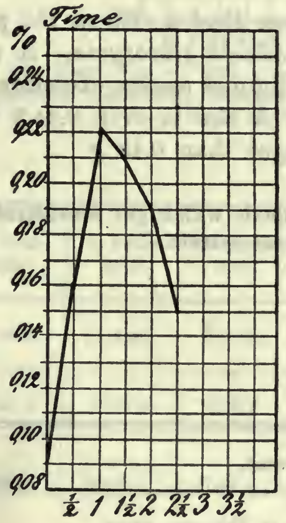

Fig. 20. Test $^{23}/_{5}$ — 15 g. glucose. 0.29 g. sugar in urine.

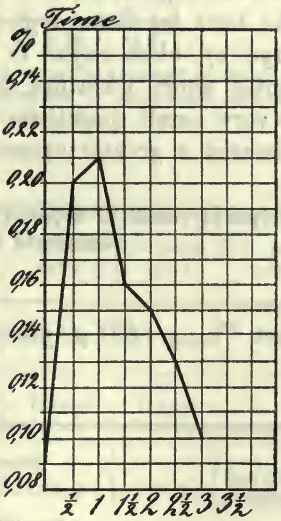

Fig. 21. Test $^{3}/_{6}$ — 10 g. glucose. 0.23 g. sugar in urine.

Urine, passed 3 hours after beginning of test (205 ccm.), reduces.

Polarimetric: 0.29 g. glucose. Passed later 390 ccm., free from sugar.

Test $^{3}/_{6}$ — *10 g. glucose.*

Table 62.

Blood-sugar, per cent.						
Before the test	After 10 g. glucose in 50 ccm. water.					
	$^1/_2$ hour later	1 hour later	$1^1/_2$ hours later	2 hours later	$2^1/_2$ hours later	3 hours later
0.09	0.20	0.21	0.16	0.15	0.13	0.10

3 hours after beginning of test passed 125 ccm. urine, which reduces. Polarimetric: 0.23 g. glucose. Passed later 460 ccm. urine, free from sugar. Percentage of blood-sugar reaches 0.21 %. (Table 62, Fig. 21.)

The tests on these dogs have shown that a rise in the percentage of blood-sugar to 0.19 % produces glucosuria. A rise of quite short duration to higher figures causes excretion of only very small quantities of sugar. A rise to even 0.24 % has not caused a greater excretion of sugar than 0.48 g.

e. Hyperglycemia in depancreatised animals which got considerable glucosuria in the tolerance-tests.

Dog II.

Test $^{22}/_{11}$ — *150 g. glucose.*

Table 63.

Blood-sugar, per cent.							
Before test	After 150 g. glucose in 750 ccm. water.						
	1 hour later	2 hours later	3 hours later	$4^1/_2$ hours later	$5^1/_2$ hours later	$6^1/_2$ hours later	$7^1/_2$ hours later
0.09	0.19	0.21	0.22	0.22	0.19	0.10	0.09

The blood-sugar determinations were made up to $7^1/_2$ hours after the beginning of the test. The results are shown in Table 63 and Fig. 22. The urine was taken with the catheter immediately after each blood-test. The bladder was washed out each time with distilled water. The results of the determinations of sugar in the urine-tests are presented in Table 64.

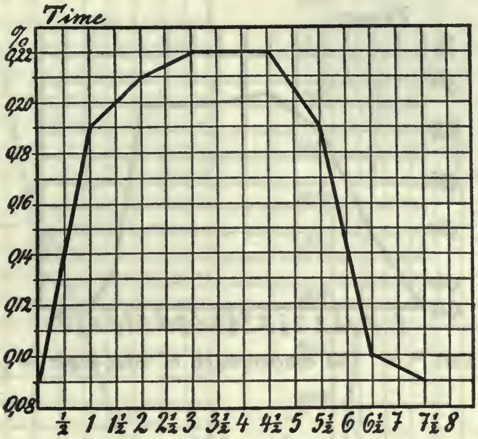

Fig. 22. Test $^{22}/_{11}$ — 150 g. glucose. 2.17 g. sugar excreted in urine. The simultaneous relationship between the concentration of urine-sugar and blood-sugar is represented in Fig. 23.

Table 64.

1 hour later	2 hours later	3 hours later	$4^1/_2$ hours later	$5^1/_2$ hours later	6 hours later	$6^1/_2$ hours later
15 ccm.	11 ccm.	9 ccm.	78 ccm.	123 ccm.	75 ccm.	
0.41 %	0.80 %	0.93 %	0.90 %	0.90 %	0.21 %	
0.06 g.	0.08 g.	0.08 g.	0.70 g.	1.10 g.	0.15 g.	free from sugar

Total excretion of glucose in urine 2.17 g.

Although the hyperglycemia is not greater than 0.22 %, the glucosuria is greater than in earlier tests where the hyperglycemia was higher than 0.22 %. This may be explained by the fact that the blood-sugar percentage remains for a longer time ($5^1/_2$ hours) at the glucosuria-producing levels. *The degree of glucosuria (i. e. the total excretion of sugar) evidently depends less on the extent of the hyperglycemia than upon its duration for values over 0.17 %.* The curve for urine-sugar concentration, nevertheless lies parallel to that for blood-sugar concentration (Fig. 23).

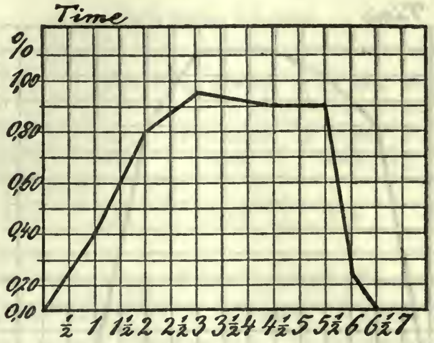

Fig. 23. Test $^{22}/_{11}$. The concentration of urine-sugar in percentage.

Dog III.

Test $^{27}/_{5}$ — *100 g. glucose.*

Table 65.

Blood-sugar. per cent.								
Before test	After 100 g. glucose in 500 ccm. water.							
	$^1/_2$ hour later	1 hour later	$1^1/_2$ hours later	2 hours later	$2^1/_2$ hours later	3 hours later	4 hours later	5 hours later
0.09	0.24	0.28	0.30	0.26	0.21	0.20	0.14	0.10

Already after half an hour the blood-sugar percentage has reached a level of 0,24 %. The highest value is reached after $1^1/_2$ hours with 0.30 %.

The hyperglycemia remains for 3 hours at the glucosuria-producing levels, after which it rapidly sinks. (Table 65, Fig. 24).

The urine passed 5 hours after beginning of test (265 ccm.) contains 0.94 % glucose, equal to 2.49 g. Urine passed later is free from sugar.

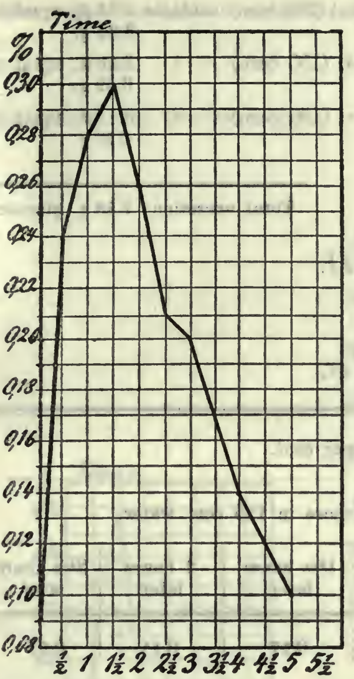

Fig. 24. Test $^{27}/_{5}$ — 100 g. glucose.
2.49 g. sugar in urine.

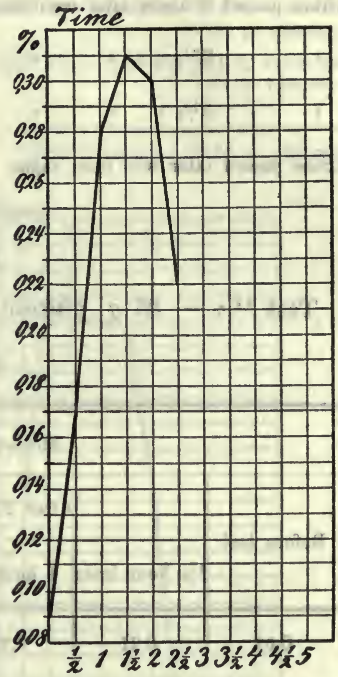

Fig. 25. Test $^{10}/_{5}$ — 50 g. glucose.
7.83 g. sugar in urine.

Dog II.

Test $^{10}/_{5}$ — *50 g. glucose.*

Table 66.

Blood-sugar, per cent.					
Before test	After 50 g. glucose in 250 ccm. water.				
	½ hour later	1 hour later	1½ hours later	2 hours later	2½ hours later
0.09	0.17	0.28	0.31	0.30	0.22

The concentration of blood-sugar rises to 0.31 % 1½ hours after injection. (Table 66, Fig. 25).

Urine passed 2 hours after beginning of test (260 ccm.) contains 1.53 %, equal to 3.92 g.
» » $2^{3}/_{4}$ » » » » » (150 ccm.) » 2.46 %, equal to 3.69 g.
» » $5^{1}/_{4}$ » » » » » (120 ccm.) » 0.18 %, equal to 0 22 g.

Urine passed later free from sugar.

Total excretion: 7.83 g. glucose.

Dog II.

Test $^{11}/_{5}$ — *25 g. glucose.*

Table 67.

Blood-sugar, per cent.					
Before test	After 25 g. glucose in 125 ccm. water.				
	$^{1}/_{2}$ hour later	1 hour later	$1^{1}/_{2}$ hours later	2 hours later	$2^{1}/_{2}$ hours later
0.08	0.21	0.26	0.17	0.11	0.09

Urine passed $2^{1}/_{2}$ hours after beginning of test (240 ccm.) contains 0.57 %, equal to 1.36 g. glucose. Urine passed later free from sugar. The hyperglycemia is considerable, 0.26 %, but of short duration. (Table 67, Fig. 26.)

It appears from these, as from previous tests, that both the degree of hyperglycemia and its duration are of importance in determining the amount of glucosuria. Of these two factors, however, the latter seems to be the most important.

Test $^{25}/_{5}$ — *100 g. glucose.*

Table 68.

Blood-sugar, per cent.									
Before test	After 100 g. glucose in 500 ccm. water.								
	$^{1}/_{2}$ h. later	1 h. later	$1^{1}/_{2}$ h. later	2 h. later	$2^{1}/_{2}$ h. later	3 h. later	$3^{1}/_{2}$ h. later	4 h. later	5 h. later
0.08	0.23	0.25	0.34	0.34	0.38	0.33	0.27	0.17	0.12

Urine passed 1$^{1}/_{2}$ h. after beginning of test (350 ccm.) contains 2.65 %, equal to 9.27 g. glucose.

» » 5 » » » » » (320 ccm.) contains 2.36 %, eqnal to 7.55 g. glucose.

Urine passed later free from sugar.

Total excretion: 16.82 g. glucose

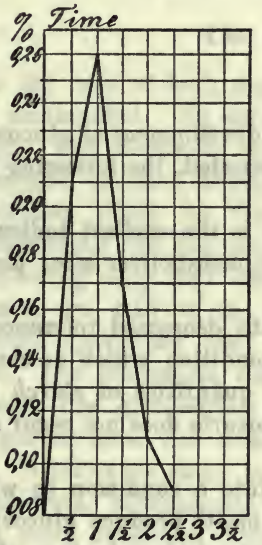

Fig. 26. Test $^{11}/_{5}$ — 25 g. glucose.
1.36 g. sugar in urine.

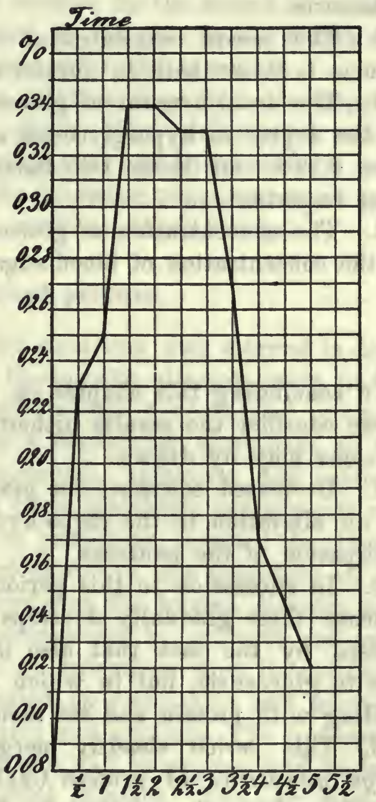

Fig. 27. Test $^{25}/_{5}$ — 100 g. glucose.
16.82 g. sugar in urine.

This test was made on the dog in stadium decrementi. *On the same dog a test was made half a year before with the same quantity of glucose, 100 g.* ($^{27}/_{10}$). *Whereas on that occasion the hyperglycemia did not rise higher than to 0.22 %, and in the urine there was excreted only 0.27 g. glucose* (BANG), *the hyperglycemia now rises to 0.34 % (Table 68, Fig. 27) and 16.82 g. glucose is excreted in the urine.* Apart from this, the dog presents nothing of pathological interest. The amount of blood-sugar in a fasting state is normal, 0.08 %, and there is no spontaneous glucosuria.

From these determinations regarding blood-sugar it appears:

1. The percentage of blood-sugar, which normally is from 0.08 % to 0.09 %, can rise to 0.17 % without the occurrence of glucosuria.
2. The lowest concentration of blood-sugar producing glucosuria is 0.19 % both in normal and operated animals.
3. The total amount of glucose excreted is dependent both on the degree of hyperglycemia and on its duration for values over 0.19 %. Of these two factors the latter seems to be the most important.
4. The concentration of glucose in the urine is proportional to the concentration of blood-sugar.

In concluding this chapter on the development of glucosuria if we consider the results hitherto recorded, the following conclusions may by drawn:

1. Decreased tolerance for *glucose* is the earliest indication of an alteration in the carbo-hydrate metabolism after partial extirpation of the pancreas.
2. In succession to this period with decreased tolerance for glucose there gradually develops a condition which is characterised by the fact that also large quantities of *starch* give rise to glucosuria, but in which glucosuria does not occur after feeding with protein and fat alone.
3. This period steadily merges into a condition in which *large quantities of protein* (300 g. meat) produce glucosuria, but in which the glucosuria disappears on reduction of the quantity of protein (100 g. meat).
4. The glucosuria then further develops itself and is manifest also after *small quantities of protein* (100 g. meat).
5. In the end, even after fasting-days, the glucosuria can be got to disappear only with difficulty, or not at all.

The manifest Diabetes.

From the operation till the diminution of the tolerance, or till the appearance of the spontaneous glucosuria, there elapsed in the case of the 4 dogs operated on a time of very different duration. For the first dog 9 months, for the second 19 months, for the third 10 months, whilst in the case of the fourth dog glucosuria appeared immediately after the operation.

In the first and the last of these dogs there developed a chronic diabetes, ending in death after a further 8 and 13 months respectively. The conditions and the metabolic tests, which shall be described in the following pages, are based upon observations and experiments made on these 2 dogs.

The clinical picture.

In the case of both dogs the condition was allowed to develop unhindered. No special therapeutic attempts were undertaken. The metabolic experiments that were carried out were calculated to have, sometimes a favourable, sometimes an unfavourable effect on the glucosuria, ketonuria and acidosis. Disregarding for the present these metabolic experiments and considering only that which in pathology is called the clinical picture, we find in the development of this condition all the cardinal symptoms that characterise the human diabetes mellitus. The glucosuria was accompanied by polyuria and polydipsia. The glucosuria's gradual transition from the milder to the graver form was accompanied by emaciation and polyphagia. Afterwards came ketonuria and acidosis. The companion of acidosis, albuminuria did not fail to appear, and in both dogs there developed double-sided cataract. The only dissimilarity presented by the clinical picture as compared with diabetes mellitus was in the manner of death. Neither of the dogs got coma. They both died in a marastic state and were fully conscious to the last. None of the distinguishing marks of coma were present.

1. The glucosuria.

Clinically we distinguish three forms of glucosuria: The mild glucosuria, the medium-grave and the grave form [v.

Noorden (42)]. All three forms have been observed. During the progress of the disease these forms have followed each other with gradual transition from the mild to the medium-grave and to the grave form, so that the course of the disease can be divided into periods corresponding to these forms.

The mild form is according to v. Noorden, characterised by the fact that it disappears on removal from the diet of carbohydrates, without it being necessary at the same time to limit the usual quantity of protein. The form was observed in the case of all 4 dogs and has been described in detail in the previous chapter on the development of the glucosuria.

After the glucosuria was manifest also on a diet consisting exclusively of protein (meat), it appeared in *the medium-grave form.* This form is characterised by the fact that the urine does not become free from sugar on a diet free from carbohydrates, but rich in protein. But by a moderate reduction of the supply of protein the urine is rendered free from sugar. This stage was observed in the case of dog IV and is described in detail in the foregoing chapter.

This medium-grave form, however, rapidly passed over to *the grave form*, which is characterised by the fact that the glucosuria does not disappear even after a considerable reduction in the supply of protein or even after fasting. Both dogs lived for 8 months with the grave form of glucosuria.

The condition of the glucosuria during the different metabolic experiments will be dealt with later on.

2. Diuresis.

The tolerance-tests with glucose occasioned every time a huge increase in the diuresis. Dog III, however, forms an exception. In this dog no diuretic effect from the glucose was noticed, even after the largest doses (23 g. per kg.). The glucosuria in this dog was never accompanied by polyuria. The circumstance reminds us of the not infrequent cases of diabetes decipiens in the human being, although the conditions are not entirely congruent, seeing that this dog never had spontanenous glucosuria. On the other hand, the other dogs often had extreme diuresis under tolerance-tests that did not bring on glucosuria.

Simultaneously with the spontaneous glucosuria there appeared polyuria. The highest degree of spontanenous diuresis observed was 2685 cubic centimetres in a dog weighing 10.65 kg., which is 1/4th of the body-weight. On an ordinary meat-fat diet the diuresis was from 1/10th to 1/5th of the body-weight.

3. Weight.

The dogs operated on when puppies increased in weight just like the other, non-operated, dogs of the same litter. The first male-dog operated on was actually the largest and strongest of the whole litter, right up to the appearance of the spontaneous glucosuria. The absence of the pancreas has therefore not occasioned any under-nourishment by reason of defective absorption.

Dog I increased in weight from 3.70 kg. at the operation to 17.20 kg. half a year later. The dog was then about $9^1/_2$ months old and full-grown. It remains at that weight for fully 3 months longer, until it gets spontaneous glucosuria. It then decreases rapidly in weight down to about 11 kg. Afterwards it loses weight more slowly, about 1 kg. every month. The diet was usually 200 g. horse-flesh and 120 g. fat. The melting-point of the fat was about 25° C. and it was emulsified with 2 $cm.^3$ 10 % Na_2Co_3. Five months after the appearance of the glucosuria the weight has sunk to 7.60 kg. At this point it gets first 500 g. and afterwards 700 g. horse flesh, whilst the fat is reduced to 50 g. The fat is now emulsified with 10 $cm.^3$ 10 % Na_2Co_3. The dog thereby increased steadily in weight, became more lively and buoyant, whereas at the close of the foregoing period it was almost cachectic. In the course of 1 month it gained 1 kg. in weight. During this time it had a daily sugar-excretion of about 40 g. glucose. The increase in weight may be assumed to be due to a better absorption owing to the fat being emulsified with more soda. The emulsion was thereby enabled to maintain itself better while passing through the ventricle. The change, that took place in the dog in the course .of that one month, was amazing. Whereas, for some time before it had hardly been able to raise itself or to get over a doorstep, it can now easily hop up on the scales and jump around on the floor, lively and buoyant. Whether this change is due to the alkali-treatment or to the better absorp-

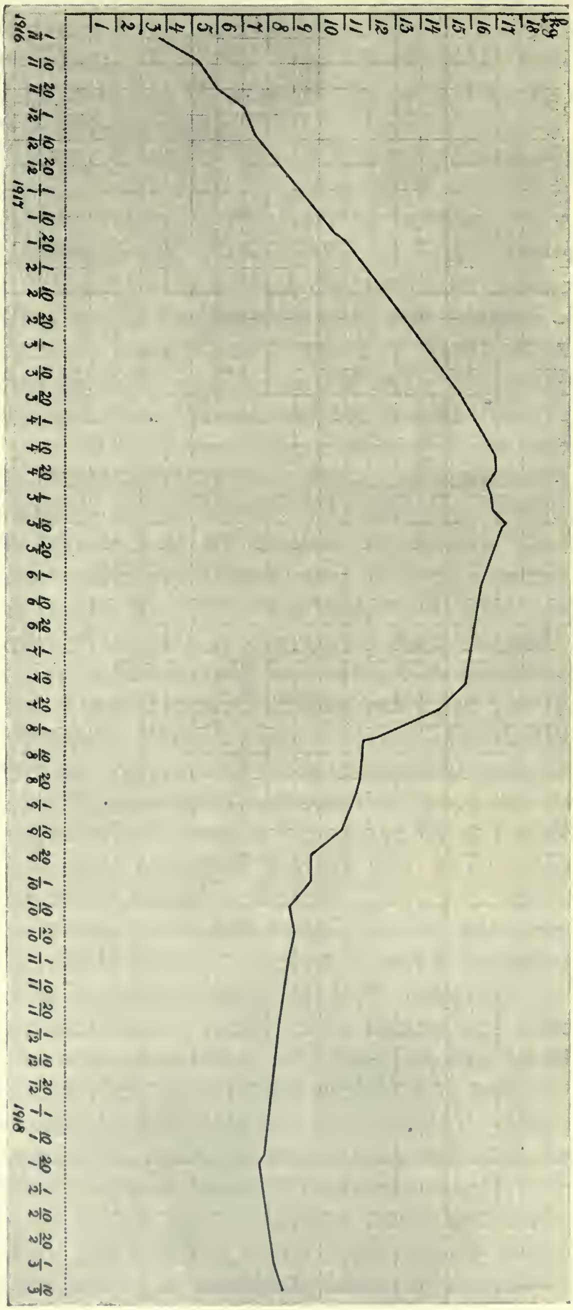

Fig. 28. Weight-curve. Dog I.

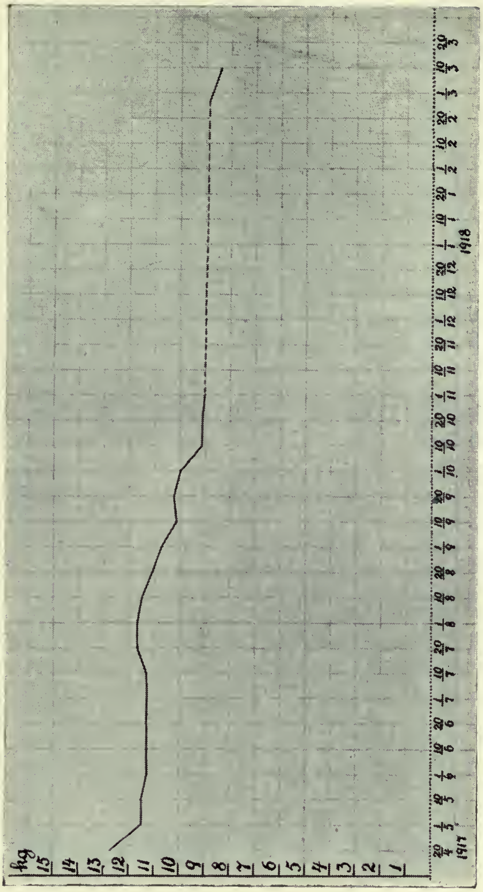

Fig. 29. Weight-curve. Dog IV.

tion cannot be decided, probably it is due to both. The dog died, however, shortly after. Perhaps the long-continued administration of soda brought on the affection of the intestine which was the probable cause of death (see chapter on post-mortem findings).

Dogs II and III gained in weight after the operation exactly like dog I. Dog II, however, which was entirely without pancreas-juice in the intestines, was all the time smaller and thinner than the other dogs of the same litter.

Dog IV, which was operated on when full-grown, and in which the glucosuria appeared immediately after the operation,

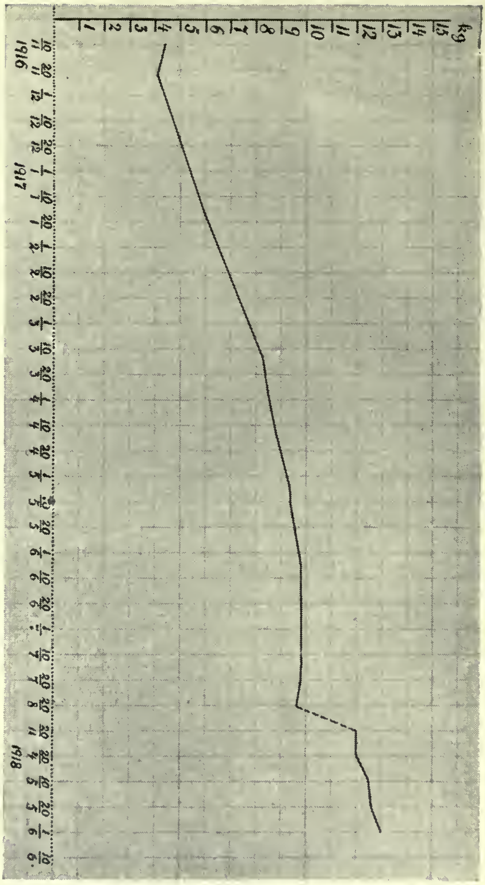

Fig. 30. Weight-curve. Dog II.

at once began to lose weight. In the course of 1 year it decreased steadily in weight from 13 kg. down to 6.40 kg. Like the first dog it was in the end only skin and bone. The absorption became worse and worse. Shortly before it died an absorption-test was made, which showed, that it absorbed badly both meat and fat.

Coprophagia was observed in both of the diabetic dogs.

The weight-conditions in all 4 dogs is graphically represented in Fig. 28, 29, 30 and 31.

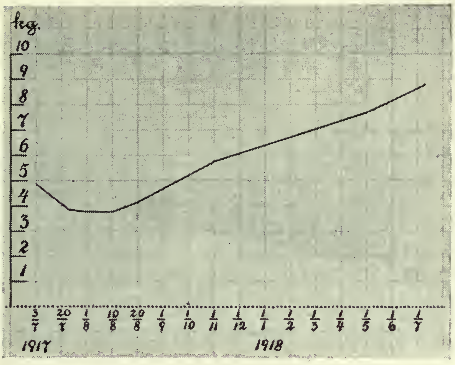

Fig. 31. Weight-curve. Dog III.

4. Hyperglycemia.

In the experiments regarding blood-sugar in these diabetic animals in the course of a long period, during which the dogs were fed exclusively on meat and fat, it was observed that the percentage of blood-sugar might vary considerably from day to day, in spite of the fact that the dogs got the same diet and the glucosuria did not change. The blood-tests were then made sometimes before and sometimes after feeding. In fasting animals the amount of blood-sugar was from 0.15 % to 0.20 %, after a meal it was from 0.20 % to 0.30 %.

Blood-sugar tests made on human diabetics by JACOBSEN [(39) p. 140] have not shown any increase in the percentage of blood-sugar after a protein-fat diet. In the blood-sugar tests made on these diabetic dogs it was proved that an increase took place after feeding with protein-fat (Tables 69 and 70):

Table 69.

Dog I.

Test 7/10.

Amount of blood-sugar when fasting	0.15 %
» » » 1 h. after 200 g. horsebeef + 200 g. fat	0.25 %
» » » 2 h. » 200 g. » + 200 g. »	0.25 %
» » » 3 h. » 200 g. » + 200 g. »	0.23 %
» » » 4 1/2 h. » 200 g. » + 200 g. »	0.22 %

Table 70.

Dog IV.

Test $^{28}/_{10}$.

Amount of blood-sugar when fasting	0.15 %
» » » 1 h. after 200 g. horsebeef + 120 g. fat	0.24 %
» » » 3 h. » 200 g. » + 120 g. »	0.23 %
» » » $4^1/_2$ h. » 200 g. » + 120 g. »	0.20 %

As the increase in the blood-sugar comes so soon after feeding, and as the percentage of blood-sugar begins to sink while absorption is still proceeding, one should be inclined to suppose that there are perhaps other factors at work besides the mere absorption of the digested food. The conditions of digestion in these depancreatised dogs are, of course, widely different from the conditions in normal animals and in human diabetics. Since the pancreatic juice is lacking, the sour gastric juices will render the contents of the duodenum sour. An action of chemical nature on the liver, resulting from the absorption of the sour contents of the intestine with consequent increase in the concentration of hydrogen-ions in the blood of the portal vein, cannot be excluded. In order to find out whether the ventricle-secretion has any influence on the concentration of blood-sugar, the following experiment was made: The amount of blood-sugar was determined in a fasting dog. Afterwards the stomach-tube was introduced into the empty stomach in order to investigate the effect of mechanical irritation on the mucous membrane of the stomach. The amount of blood-sugar was then determined after $^1/_4$ and $^1/_2$ hour (Table 71):

Table 71.

Dog I.

Test $^{29}/_{10}$.

Amount of blood-sugar when fasting	0.20 %
» » » $^1/_4$ h. after introduction of stomach-tube	0.23 %
» » » $^1/_2$ h. » » » »	0.25 %

Immediately after this period 300 cubic centrimetres of water were introduced by means of the stomach-tube, and the amount of blood-sugar was determined after the lapse of 5 minutes, half an hour and 1 hour (Table 72):

Table 72.

Amount of blood-sugar 5 minutes after	0.26 %
» » » $^1/_2$ hour »	0.26 %
» » » 1 hour »	0.23 %

The concentration of blood-sugar shows a perceptible increase both after the mere introduction of the stomach-tube and in a still higher degree after the administration of water (Tables 71 and 72). The dog has in the last few months been fed daily by means of the stomach-tube. It is so accustomed to it that it sits quietly on the floor while the tube is being introduced, it does not resist and does not need to be held. It is altogether very phlegmatic, submits to every investigation and does not mind the prick in the ear. It seems therefore to be out of the question that the increase in the amount of blood-sugar can be due to affectional causes (BANG).

Immediately after the foregoing test 300 cubic centimetres of bouillon were administered:

Table 73.

Amount of blood-sugar $^1/_4$ hour after	0.25 %
» » » $^1/_2$ » »	0.29 %
» » » $^3/_4$ » »	0.30 %
» » » $1^1/_2$ hours »	0.28 %
» » » $3^3/_4$ » »	0.26 %

There is a distinct increase already after $^1/_4$ hour from 0.23 % to 0.25 %, and after $^3/_4$ hour the concentration of blood-sugar has risen right up to 0.30 % (Table 73). In this test the influence of protein, poly-peptides and amino-acids present in the bouillon cannot be ignored. Moreover, the bouillon contains reducent elements (creatinin, purines), which are absorbed and possibly can increase the reducent capacity of the blood.

In order to find out whether the reducent substances contained in the bouillon could bring about this result of the blood-sugar tests, the effect of bouillon on normal dogs was investigated:

Table 74.

Dog VI.

Foxterrier, male, full-grown.
Test $^{31}/_{10}$.

Blood-sugar when fasting	0.10 %
» $^1/_2$ h. after 300 cm.^{3} bouillon (stomach-tube)	0.11 %
» $^3/_4$ h. » » » »	0.11 %
» $1^1/_2$ h. » » » »	0.10 %

The increase is minimal (Table 74) and is not sufficient to explain the great increase in the case of the sick dog. Moreover, the increase lies inside the margin of error of the method and can also be due to psychical effects in the less practised dog.

The increase was greater in a dog that was depancreatised, but not yet diabetic:

Table 75.

Blood-sugar when fasting	0.10 %
» $^1/_4$ h. after 300 cm^3 bouillon (stomach-tube)	0.12 %
» $^1/_2$ h. » » » »	0.13 %
» $^3/_4$ h. » » » »	0.11 %
» $1^1/_2$ h. » » » »	0.09 %

The increase in blood-sugar is not great, but yet distinct, from 0.10 % to 0.13 % (Table 75).

The tests with bouillon have thus shown a considerable increase of hyperglycemia in a pancreas-diabetic dog, a distinct increase in blood-sugar in a depancreatised, but non-diabetic dog, but no increase in a healthy dog.

Feeding-tests with protein-fat show an increase of blood-sugar in 2 diabetic dogs. The increase coincides with the termination of the ventricular digestion and the emptying of the ventricle, and has attained its highest point before the absorption is finished.

The test with administration of water and even with mechanical irritation of the ventricle by the stomach-tube (psychical secretion, introduction of the stomach-tube in a fasting animal) show a distinct increase of hyperglycemia in diabetic animals.

If we search in the literature for other observations that can afford an explanation or a support for those mentioned here, we shall find that several investigators in the most recent time have been aware of the influence exerted by ventricular secretion on the effects of pancreas-extirpation.

Murlin & Sweet (43) find that pylorus exclusion or gastrectomy diminish the effects of total pancreatectomy. In such an operation the removal of the gastric juice from the intestine is of course the most essential change from the usually prevailing conditions. In 3 dogs, in which the pylorus was ligated simultaneously with the total pancreatectomy, no glucosuria appeared in the course of the first 24 hours, and in the case of 5 dogs, on which gastrectomy had first been performed, there occurred no or only slight glucosuria after the removal of the pancreas.

MURLIN & SWEET's observations seem capable of providing an explanation of my observation. The increase in the percentage of blood-sugar after a meal free from carbo-hydrates, after bouillon and even after water, is due perhaps to the fact that absorption of hydrochloric acid in the intestine becomes possible owing to the absence of the neutralising pancreatic juice. Thereby the concentration of hydrogen-ions is augmented in the blood of the portal vein, which in its flow through the liver might be supposed to affect the glycogen in the liver with the result that hyperglycemia occurs. That water has a directly stimulating influence on the secretion of gastric juice has been demonstrated by BERGEIM, REHFUSS and HAWK (44). On the other hand, a mechanical irritation will not occasion any secretion of gastric juice. The effect of the stomach-tube on the empty stomach must therefore probably be due to psychical secretion. The dog was hungry; it received every day fat-emulsion through the stomach-tube and immediately thereafter meat. The introduction of the stomach-tube has possibly aroused in the animal anticipations of the approaching meal of meat, and thereby the psychical secretion has been started. The probability of this explanation is strengthened by the fact that immediately after the removal of the stomach-tube the dog at once sprang towards the dish containing meat.

The tests seem to give an insight into the mechanism of the occurrence of hyperglycemia and glucosuria in depancreatised dogs. The external pancreatic secretion is not without significance in so far as it is capable of neutralising the gastric juice. But the complete absence of pancreatic juice is not, however, tantamount to the dog's getting hyperglycemia, cf. the depancreatised but non-diabetic dog III. As long as the internal function is in order, the absence of the external secretion will be of less importance. Provided this view of the matter is correct, it seems that we may draw the conclusion that one of the properties of the internal pancreatic secretion must be the power of reducing the concentration of hydrogen-ions, in other words, it has the character of an alkali. Murlin & Sweet draw the same conclusion from their experiments. On the basis of the tests that have been described in this work, we shall not, however, attempt to give any more exact characterisation of the *chemical* properties of the internal pancreatic secretion. Later on, under the general considerations we shall try to give an explanation of the mechanism of the occurrence of hyperglycemia and glucosuria.

5. Acidosis.

In both of the diabetic dogs there appeared in the course of the disease acidosis, characterised by increase in the amount of the ammonia-figure [Percentage ammonia of total nitrogen, Hasselbalch (45)], sinistral rotation of the fermented urine and positive aceton and acetic-acid reaction in the urine. In one of the dogs, which was operated on when a puppy, the acidosis occurred shortly after the appearance of the glucosuria. The condition may best be described as a severe diabetes already from a short time after the glucosuria was manifest. The dog had the whole time until the glucosuria appeared and for some time after lived on a diet rich in carbo-hydrates. Simultaneously with the appearance of the glucosuria there began a rapid emaciation, from 16 kg. to 12 kg. in the course of a month. Some days after its being put on a diabetic diet (horseflesh and fat) Lieben's & Gerhardt's reactions were positive, and the urine had sinistral rotation after fermentation, which had not been the case before, and the amount of ammonia began to rise. During the further course of the illness the acidosis increased. An ammonia-figure of over 30 was observed (Oct. 4th), whereas the ammonia-figure in a dog without acidosis is from 3 to 5. The fermented urine showed increased sinistral rotation, and the odour of aceton distincly increased, ferric-chloride produced a dark burgundy-colour, at times almost black (indicated in the protocols by + +). On the days, when the highest ammonia-figure was noted, about 2 g. aceton (total-aceton) were excreted. P_H lay at that time, as for the rest during the whole course of the disease, between 6 and 7. Greater acidity in the urine than $P_H = 5.40$ has not been observed.

Just as in the case of dog I[illegible], the acidosis distinctly diminished on feeding with small quantities of dried hypophysis. Both dogs had lipæmia (opaque serum).

Thus, whilst in the case of the first dog operated on acidosis was present during the whole course of the diabetes, lasting 8 months, in the second dog, operated on when full-grown, no sign of acidosis could be observed in the first 3 or 4 months after the glucosuria appeared. In this latter dog there was a loss of fully 1 kg. in weight just after the operation. But after that the equilibrium of nutrition maintained itself for nearly 4 months. At the same time that signs of acidosis appeared, the weight began to decrease. According as the emaciation proceeded, the ketonuria and the ammonia-figure increased. The dog was given the same number of calories as before (taking into account the glucosuria); the absorption was no worse than before. And yet it lost flesh. Also in the case of dog I there was rapid emaciation simultaneously with the appearance of acidosis. This circumstance suggests the question whether the acidosis was the result of mal-nutrition, which again might itself be due to augmented metabolism. Or whether the augmented metabolism was the consequence of the acidosis [BENEDICT & JOSLIN (62)]. These questions will be discussed later on in the chapter on the total metabolism.

Some authors have maintained that pancreatic diabetes in dogs is not accompanied by acidosis. BRUGSCH [(47) p. 339] and BRUGSCH & BAMBERG (48) find that there is a fundamental difference between pancreatic diabetes in dogs and diabetes mellitus in man, since they never met with pronounced acidosis in dogs. MINKOWSKI, however, observed acetonuria in some of his diabetic dogs, and both of SANDMEYER's dogs had some days a slight acidosis with acetonuria. Subsequently, acidosis in connection with pancreatic diabetes has been described by ALLARD (49) and by ALLEN (22), (72). ALLARD is the only author that mentions dogs dying in coma. As a rule, these dogs die in a cachectic state without any coma being observed. Neither did any of our dogs get coma. On one single occasion there was observed in one of the dogs respiration of KUSSMAUL's type.

This difference in the manner of death in pancreatic-diabetic dogs and in human diabetics, which has thus been established as a rule, seems to be capable of contributing to the solution of the question whether the symptoms of the coma are due to the acidity of the ketones or to the chemical action of these substances on the brain or to both factors together. In these dogs there were no symptoms of acid-poisoning. On the other hand, there was considerable ketonuria in proportion to the size of the dogs. Since, as has been stated, coma did not occur, it may be assumed that it is the acidity that is the most essential cause of the symptoms of coma, unless indeed the canine brain reacts in the presence of the ketones in a different manner than the human brain. It is, however, possible that the difference is due to a peculiarity in the nature of the canine brain. It is a well-known fact that dogs stand large doses of morphia, and that much larger doses are required to produce narcosis with morphia in a dog than in a human being. Something similar may be the case with respect to the ketones.

6. Albuminuria.

Albuminuria is of quite frequent occurrence amongst diabetics. In both of the diabetic dogs albuminuria appeared in the course of the disease. In dog I about 2 months, in dog IV about 6 months after the glucosuria arose. The albuminuria was at first very slight, only a trace, but it afterwards increased in intensity. In both dogs it appeared after the ketonuria had lasted for some time, and it gradually became greater according as the acidosis increased. During the tests with hypophysis-feeding the albuminuria declined until there was only a trace. At the same time the diuresis, glucosuria and ketonuria diminished. Whether a single one of these factors or several combined was the cause of the injury to the renal epithelium, which is the fundamental cause of the albuminuria, cannot be decided.

7. Cataract.

Artificial cataract in animals induced by injection of sugar and various salts has been described by several authors. In a frog cataract has been induced by WEIR MITCHELL (50) by injection of a solution of sugar into the dorsal lymphatic pouch. If the frog was placed in a sufficient quantity of water the cataract failed to appear. DEUTSCHMANN (51) and HEUBEL (52) have attained positive results on a number of animals with the aid of sugar and various salts. (Injection in the camera ant. or by placing the lens after removal in concentrated solutions.) More recent investigators, however, are not inclined to regard as genuine cataract these artificially produced obscurations of the lens. Thus, PINELES (53) is of the opinion, that the cause of the diabetic cataract, as well as of tetanic and senile cataract, lies in the special metabolic changes arising from the endocrine glands.

In experimental pancreatic diabetes cataract does not seem hitherto to have been observed. In both of our dogs cataract occurred. As it is therefore probably the first time that this affection of the eye is recorded in pancreatic-diabetic dogs, and as it is very interesting from a comparative pathological point of view, those extracts from the journal that concern cataract are set down here.

Dog I.

$^{15}/_{11}$ 1917.

In the course of the past month the dog's sight has begun to be defective. First it was noticed, that the dog did not, as before, snatch with certainly at a piece of meat held before it, but searched for it with the muzzle. About 2 weeks ago there was observed an obscuration of the lens in the left eye, and last week also in the right eye. An ophthalmological examination was to-day kindly made by Dr. AKSEL UCHERMANN, Assistent in the Eye Department of the State Hospital, who describes the result as follows:

O. u. The environs of the eyes normal. Nothing to remark about mobility, eye-lids and cilia. Conjunctivae palpebrae & bulbi pale. Corneae smooth, reflectant, transparent.

O. d. Camera anterior: Shallow in centre, but in the periphery of same depth as in left eye. Contents clear.

Iris: Distinct markings, lustre good.

Pupil: 5.5 mm. round. Good reaction both for light and for convergence. In the pupillary field, completely filling it, there is seen lying right up to the edge of pupil a greyish obscuration, faintly shimmering like mother-of-pearl, which presents a sector-formed structure. Downwards and inwards two very small stripes of a somewhat duller grey (cataracta incipiens). With penetrating light a faint light-red reflection is obtained on looking straight forward, on looking in other directions a faint greenish-blue reflection. There are seen, besides, dark striped obscurations without definite arrangement.

Back of eye cannot be seen.

Projection good in all directions.

O. s. Camera anterior: just a little shallower in the centre than on the periphery. Contents clear.

Iris: Distinct markings, lustre good.

Pupil: 5.5 mm. round. Good reaction both for light and for convergence. In the pupillary field, completely filling same, there is seen an even, homogeneous obscuration, lying right up to the edge of pupil. With a penetrating light there is seen upwards and inwards in a small aperture a faint light-reddish reflection. Otherwise only grey reflection (matura).

Projection: Good in all directions.

Tension o. u. Soft on palpation with finger.

The cataract in the right eye increased. A month later it was completely blind, although sensitive to light. During the three months it still lived, the dog got conjunctivitis, and it seemed that the sensitiveness to light also decreased.

Dog No. IV.

7/5 1918.

During the last few weeks there has been observed an increasing obscuration of the right pupil. Ophthalmological examination to-day (Dr. A. UCHERMANN) gave the following result:

O. u. Conj. palp. & bulbi pale.

Corneae: Even, reflectant, transparent.

Camera anterior: Of considerably less depth on the right side than on the left. Contents clear.

Iris: Distinct markings.

O. d. Pupil about 7 or 8 mm. round. Good reaction. In the pupillary field, completely filling same, there is seen a greyish-white, shapeless obscuration, shimmering like mother-of pearl, close behind the edge of pupil, so that the iris casts no shadow. Good reflection with penetrating light. The back of the eye is not seen.

Visus: Good sensibility to light.

Field of vision: Looks after the light in all directions.

Tension: Soft on palpation with finger.

O s. Pupil: 7 or 8 mm. round, black. Good reaction. With penetrating light good, greenish reflection. Inwards in the pupillary field about 3 or 4 mm. from the edge of the pupil there is seen a dark, striped obscuration, 0.5 cm. broad, lying in the posterior cortex of the lens.

The back of the eye is clearly seen, both papillae and blood-vessels.

Visus: Good sensibility to light.

Field of vision: Looks after the light in all directions.

Tension: Soft on palpation with finger.

In the course of a week there was complete obscuration also of the left lens. The dog was afterwards completely blind, but with good sensibility to light.

In the case of the first dog the cataract was a symptom that appeared rather early, as it occurred only a couple of months after the glucosuria was manifest. The second dog, on the other hand, was diabetic for a whole year before it got cataract. Only a very short time elapsed from the first slight obscuration of the lens, until the cataract was ripe. Both animals were young, about 2 years old when they died.

Metabolism.

1. The total metabolism.

The object of investigations regarding the total metabolism in diabetes has been to solve the following two main problems in diabetic research:

1. Are the total metabolism and the transformation of energy in diabetes increased, diminished or normal?

2. Is the production of sugar in diabetes augmented, or is the consumption of sugar reduced, or is there at the same time both an increased production and a diminished consumption?

The first question has been investigated in human diabetics by Pettenkofer and Voit (54), who found that in diabetes the consumption of oxygen was diminished; by Weintraud & Laves (55), who observed a diminished metabolism in severe cases; by Leo (56), Stüve (57), Nehring & Schmoll (58), Magnus-Levy (59) and Mohr (60), all of whom found an increased metabolism among grave diabetics. In two extensive investigations carried out in 1910 and 1912 Benedict and Joslin (61) (62), have found an increase in the total metabolism of from 15 to 20 %. They arrive at this result after examination of the pulse frequency, the consumption of oxygen and the production of heat, which on an average were 15 to 20 % higher in individuals with grave diabetes than in normal individuals of the same size and weight. The excretion of carbonic acid, on the other hand, was increased by only 6 %, which they explain as being the result of the protein-fat diet. Leimdörfer (63) confirms Benedict and Joslin's observations as to the greater consumption of oxygen, but finds, on the other hand in contrast to them, that the excretion of carbonic acid is not increased. Rolly (64) and Grafe & Wolf (65) have results coinciding with those of Benedict and Joslin. In contrast to these authors Allen and Du Bois (67) found either none at all or else only a slight increase of the total metabolism in diabetics, and in hunger even a 20 % decrease. They admit, however, the posibility of an increased metabolism also, as they regard the level of the total metabolism as being the resultant of a number of forces that may sometimes augment and sometimes diminish the metabolism.

In pancreatic-diabetic dogs the total metabolism was first investigated by Weintraud & Laves (128). They found no difference in the consumption of oxygen before and after extirpation of the pancreas. Kaufmann (80) arrived at the same result. Falta, Grote & Staehelin (66), and Mohr (60) observed an increased metabolism. In an investigation in 1915 Moorhouse, Patterson and Stephenson (68) observed an increase of 15 to 20 % in the total metabolism in dogs with total pancreatic diabetes. Benedict and Joslin, as well as Moorhouse, Patterson and Stephenson, have found that the increase in the total metabolism coincides with an acidotic condition.

It seems to appear with fairly great certainty from the more recent investigations here mentioned that in grave diabetes there can really be found an increased metabolism. Provided we are willing to attach to observations regarding pulse-frequency, absorption of oxygen, production of heat etc. the same importance in diabetics as in normal individuals, we are forced to accept the conclusions that the authors mentioned draw from their experiments. It is, however, not certain whether such verifications can be assigned the same significance in diabetics as in normal subjects.

As regards the consumption of oxygen, it is in normal individuals the best indicator of the intensity of the metabolism. In diabetics, on the other hand, who through the urine lose large quantities of oxygen in the form of glucose and ketones, there must of course be absorbed correspondingly greater quantities of oxygen through respiration, in order that the combustion may proceed without decrease of the caloric effect. It is therefore a priori probable that diabetics with negative balance in carbo-hydrates will prove to have a greater absorption of oxygen than normal individuals. If we shall take the consumption of oxygen in diabetics as indicator of an increased metabolism, we must calculate in such a way, that the quantity of oxygen that is lost in the urine in the form of glucose and ketones is deducted from the absorption of oxygen recorded by the respiration apparatus. This BENEDICT and JOSLIN have omitted to do. If we study some of their tables concerning the loss of oxygen in the form of glucose and β-oxybutyric-acid in the cases where there is a negative carbo-hydrate balance, we find that, for example, in case K, Tables 13 and 14, Aug. 2—3, (p. 24 and 25, Publ. No. 176) there is a loss of 14.5 % of the quantity of oxygen absorbed, case N, Tables 21 and 28, Dec. 10—11, (p. 31 and 35) has a loss in the form of glucose and β-oxybutyric-acid of 23 % of the quantity of oxygen absorbed, case P, Tables 40 and 41, Sept. 25—26, (p. 42 and 43) has a loss of 6.3 %, and case X, Tables 99 and 100, Febr. 28 – Mar. 1, (p. 79 and 80) has a loss of 15 %. The oxygen-absorption is here calculated per 24 hours. In spite of this loss it must, however, be admitted that the consumption of oxygen in these diabetics is greater than in normal individuals, but it is not so large as stated by BENEDICT and JOSLIN, since these latter have not taken into account the point here mentioned. Neither do MOORHOUSE, PATTERSON and STEPHENSON make any deduction for the glucosuria in their calculations of the consumption of oxygen.

Regarding heat-production in diabetes FALTA (71) has recently given an exhaustive review of earlier works on this subject. FALTA's work develops into a searching criticism of BENEDICT and JOSLIN's investigations and results. FALTA, who in the beginning took part in BENEDICT and JOSLIN's investigations, finds that these are not satisfactory with respect to the biological arrangement of the tests. FALTA finds in the work mentioned no proof of increased heat production in diabetes and is himself of the opinion, that such an increase is not in general to be observed.

While Falta therefore does not think that an increase of the total metabolism in diabetes mellitus among human beings has been proved to exist, yet he believes, relying on the previously mentioned investigations of Falta, Grote and Staehelin (66), Mohr (60), as well as on investigations by Eppinger, Falta and Rudinger (157) and by Murlin and Kramer (73), that it may with certainty be assumed »that in the pancreatic-diabetic dog not only the metabolism of protein but also the heat-production is considerably increased, and that this increase in the heat-production only in a minor degree is due to the augmented metabolism of protein.«

How far there really exists such a difference in the metabolism of a human diabetic and of a pancreatic-diabetic dog must be left an open question. As regards the pancreatic-diabetic dog it seems to be agreed that the metabolism is increased, even though, as already stated in this chapter, objections may be brought against the application of the observations to such an extent as has been done.

In the case of our diabetic dogs a number of observations have been made, which shall be recorded here when speaking of the total metabolism. In both dogs emaciation made its appearance at the same time as acidosis and ketonuria. The glucosuria could no longer be banished by reducing the supply of protein, nor after two fasting-days. This coincidence of emaciation with acidosis, in spite of the fact that the dogs did not get a smaller number of calories in their food, and that the absorption was unexceptionable, and the loss of calories in the form of glucose was not great enough to explain the emaciation, seems to support the assumption of Benedict and Joslin (62) that the acidosis is the cause of the increased metabolism. It is, however, difficult in experiments, where as here the acidotic condition, hyperglycemia and the specific-dynamic action of protein make themselves felt simultaneously, to decide what is cause and what is effect. If both protein-fat, ketones and glucose are simultaneously »specific-dynamically active«, the rapid emaciation is explainable. Cserna and Kelemen (74) have shown that urea, sodium-chloride and glucose on intravenous injection into eventerated animals increase the gaseous metabolism, both the consumption of oxygen and the excretion of carbonic acid. In agreement with Tangl [(75) p. 26] they suppose that these substances act upon the cells in such a way that the metabolism and transformation of energy in the protoplasm are increased. There is no reason to suppose that the diabetic hyperglycemia has not the same effect on the protoplasm as an intravenous injection of glucose. The increased metabolism in grave diabetes might then be due to the specific-dynamic action of the hyperglycemia, ketonemia, protein and fat. The expression »increased metabolism« embraces then both the exothermal chemical processes and the more intense protoplasmic processes, which together bring about an increased production of heat. The pathogenesis of this increased metabolism might then be imagined as fellows: Increasing hyperglycemia. As a result of defective assimilation of carbo-hydrates in the liver formation of ketones, the effect of which is added to the metabolism-increasing effect of the hyperglycemia. To the effects of the hyperglycemia and ketonemia there is now added the specific-dynamic action of the strict diabetes-diet that has been instituted. The metabolism is thereby augmented yet a little more. A vicious circle is established. The increased metabolism demands a larger supply of calories, which is given mainly in the form of protein-fat, and this again brings about a continuance of the increased metabolism, both by its own specific action and by upholding the hyperglycemia and ketonemia.

The conclusions that it has been attempted to draw from *the respiratory quotient* with regard to the other main problem in diabetes-research, namely: *whether the sugar is burned up or not*, have not been able to solve the question, and it is hardly likely either that the point can be cleared up in this manner. As v. NOORDEN [(42) p. 237] strongly maintains, and his statement cannot be contradicted, the respiratory quotient will be governed by the original nature of the material for the eventual combustion. If, for example, fat is the sugar-forming material, and the sugar formed from the fat is burned, the respiratory quotient will be 0.7 and not 1. Investigations regarding the respiratory quotient after injection of glucose in a case where hyperglycemia and glucosuria already exist have of course no significance. FALTA, GROTE and STAEHELIN (66) found no increase in the respiratory quotient after administration of large quantities of glucose to a pancreatic-diabetic dog. VERZAR (76) finds the increase in the respiratory quotient after intravenous injection of glucose greater in proportion, as the hyperglycemia is less. With severe hyperglycemia he finds no increase. This fact reminds one of the old simile of the vessel that runs over when it is full. When the vessel is full to the brim further additions will, of course. be without effect. Where the limit lies, however, we do not yet know. But VERZAR interprets his observations in another manner. He observes an increase in the respiratory quotient with a hyperglycemia of 0.21 % and 0.27 %, but not with hyperglycemia of 0.33 % and 0.35 %, and he concludes from this that the hyperglycemia cannot be of any significance, »as this in the first cases is hardly greater than in the last«. This, however, is scarcely correct, there is surely a considerable difference in these dimensions. As shown in the first chapter, the relationship between hyperglycemia and glucosuria is a delicately working mechanism. The degree of variation in hyperglycemia with respect to the issue: glucosuria or not glucosuria, was found to be not greater than from 0.01 to 0.02 %. Something similar may possibly be the case with respect to consumption and non-consumption, and the limit lies perhaps just between 0.27 % and 0.35 %. At this limit, then, the vessel would be full, and all further additions would flow away without effect. VERZAR is right in his conclusion that sugar injected in the later stages of pancreatic diabetes does not burn. In his experiments together with KRAUSS (77) VERZAR has found that the isolated intestine of a pancreatic-diabetic dog *consumes* sugar. He concludes from all his experiments that the pancreatic-diabetic animal in some way or other consumes sugar, but that this consumption is not any combustion. Yet it is in my opinion assuming too much, when VERZAR, as the result of his demonstration of the fact that *intravenously injected* sugar does not burn, draws the conclusion that there is no combustion of sugar at all in pancreatic diabetes.

In a new work in 1918 BERNSTEIN and FALTA (76) have attempted by investigation of the gaseous exchange to prove that in diabetes the consumption of sugar is reduced or suspended. Blood-sugar tests were not carried out, still the same objections can be raised regarding this work as against the previously mentioned work of VERZAR, as well as against all others who attempt to solve this problem by determining the respiratory quotient. BERNSTEIN and FALTA have dealt exhaustively with the literature concerning this point and it therefore seems superfluous to speak of it again in this place. Quite recently FORSCHBACH and SCHÄFFER (129) on tetanisation of the diabetic muscle with normal circulation have failed to demonstrate any reduction of the total quantity of carbo-hydrates. From the experiments recorded, which, moreover, are not yet completed, it is not possible to draw any certain conclusions.

The question of consumption or non-consumption of sugar in diabetes must therefore be regarded as a problem not yet solved. My previously mentioned experiments regarding hyperglycemia when feeding with different substances seem to point in the direction of over-production.

2. The Quotient D/N.

That in diabetes mellitus there is a proportionality between protein metabolism and sugar-excretion v. MEHRING (79) has been the first to point out. MINKOWSKI (loc. cit.) has more closely investigated this proportionality in his pancreatic-diabetic dogs. In dogs with total pancreatic diabetes, which were fed exclusively with meat, he found that the ratio between glucose-excretion and nitrogen-excretion in the urine, the quotient D/N, lay between 2.62 and 3.05. The average value for all the dogs and all the tests was 2.8 (loc. cit. p. 97). The ratio was independent of the quantities of protein administered.

This constant ratio established by MINKOWSKI between sugar- and nitrogen-excretion in total pancreatic diabetes has been confirmed by the following investigators: KAUFMANN (80), LÜTHJE (81), who found, moreover, that fat and fat-acids did not cause any increase of the quotient, by MOHR (82) (the quotient not calculated), who also made the observation that the excretion of glucose and the quotient may decline after administration of fat. (130), ALMAGIA & EMBDEN (83), FALTA, GROTE and STAEHELIN (loc. cit.), who, however, found somewhat higher values for the quotient D/N than MINKOWSKI, FALTA and WHITNEY (84) and GIGON (85).

After partial extirpation of the pancreas the qoutient D/N is lower than after total extirpation. SANDMEYER (loc. cit.) found it on the average to be 2.0, and PFLÜGER (86) found 2.15.

In phloridzin-poisoned dogs LUSK and his collaborators and later a number of other investigators [Literature in LUSK (87)] have found the quotient D/N to be 3.65. MANDEL and LUSK (88) have found the same ratio also in diabetes mellitus among human beings on a meat-fat diet exclusively, and in pancreatic-diabetic dogs after extirpation of 3 gl. parathyreoideae EPPINGER, RUDINGER and FALTA (loc. cit, I p. 14) found the ratio D/N to be equal to 3.54.

These determinations of the quotient D/N in pancreatic diabetes can be supplemented by the determinations that have been made in the present work. Altogether 179 determinations have been made (see protocols). In the case of dog I altogether 64. Of these 43 were »pure« tests, i. e., after a diet consisting exclusively of meat or meat-fat, continuous during several weeks without administration of carbo-hydrates etc. The average value for D/N in these 43 »pure« tests was 3.00. In the case of dog IV there were made 115 determinations of D/N. In 13 »pure« continuous tests, during which the dog received daily only 1000 g. lean horsebeef, the average value for the quotient D/N was 3.10. The daily variations in this period were slight. The highest observed values for D/N in all tests were 4.21 in dog IV and 4.53 in dog I. After a diet consisting of 500 g. horsebeef and 1110 ccm. water dog IV excreted 66,42 g. glucose and 15.75 N. D/N equal to 4.21. After 1200 g. horsebeef and 1710 ccm. water dog I excreted 67.15 g. glucose and 14.82 g. N. D/N equal to 4.53. Otherwise, the same observation was made as had been already made by MINKOWSKI, namely: that with decreasing supplies of protein and in hunger the quotient D/N also decreases. MINKOWSKI's figure, 2.8, was verified in dogs fed with quantities of meat lying between 300 and 1000 g.

In both of our dogs there was therefore found a slightly higher quotient D/N than in MINKOWSKI's dogs with total pancreatic-diabetes. FALTA, GROTE and STAEHELIN have, as already mentioned (loc. cit.), found a somewhat higher D/N than MINKOWSKI in dogs with total pancreatic-diabetes, namely: 3.27.

The fact that our dogs after partial extirpation of the pancreas had a higher quotient D/N than MINKOWSKI found in his dogs after total extirpation, is interesting. Perhaps the explanation is to be sought for in the circumstance that our dogs had not received meat for a long time, but during their whole life, until the glucosuria appeared, had lived exclusively on bread and milk, that is to say: essentially on carbo-hydrates. Perhaps their metabolism by this mode of life has been changed in such a way that the formation of sugar from protein took place in a different manner than in the case of the meat-eating dogs.

Determination of the quotient D/N is otherwise of importance for the solution of the following two problems:

1. The maximum formation of sugar from protein.
2. Whether formation of sugar from fat takes place.

The theoretical highest possible value for D/N can, according to Pflüger and Junkersdorf [(89) p. 226] and Lichtwitz [(119) p. 125] be calculated in the following way:

100 g. meat-protein contains 16 % N and 51.8 % C.

As basis for the calculation it is presumed that all N is excreted in the form of urea.

16 g. N corresponds to 34.3 g. urea with 6.8 g. C.

For sugar-formation there should then remain 51.8 minus 6.8 equal 45 g. C, that is to say, from 100 g. protein there can at the most be formed 112 g. glucose. D/N should then be equal to 112/16 equal to 7.00.

The calculation is not quite accurate, since no account is taken of the fact that some nitrogen leaves the organism in the form of ammonia. This error in the calculation, however, is to a certain degree compensated for by the increased excretion of carbon in the form of creatinin and purines, so that the increase in the quotient that would have to be made if the ammonia-excretion were also taken into account disappears again when the excretion of creatinin and purines is included. We may therefore without substantial error reckon the N-excretion as urea. If we now take the carbon and nitrogen contained in the meat-protein as basis for calculation the maximum value of D/N will be equal to 7.00. This maximum D/N quotient in sugar-formation from protein is of importance, when we shall try to answer the question as to whether fat is a sugar-former, since it can hardly be denied that one of the things required in order to prove that sugar is formed from fat ought to be the fact that the quotient D/N is higher than 7.00.

Rubner [Gesetze (69) p. 383] calculates the maximum sugar-formation from protein in a different manner. He has found, that 1 g. N in protein only represents 18.6 calories utilisation-value, since 27.2 % of the energy-contents concists of heat-processes without energetic action. If it is now assumed that these 18.6 calories proceed exclusively from the glucose formed, then to 1 g. N there will correspond 18.6/3.74 or 4.97 g. glucose. The maximum value for D/N after this method of calculation will thus be 4.97.

Meanwhile, it is generally supposed that the protein decomposes only a certain part of the nitrogen-free remainder in the form of sugar, [Gigon (85), Landergren (90) p. 70, Rubner (loc. cit.)]. The decrease in D/N which takes place with a scanty supply of protein and in hunger (and which was observed in my experiments) seems capable of being construed in this manner. Rubner suggests (loc. cit. p. 393) that this remainder is possibly glucuron-acid, since Loewi (91) has found that in phloridzin-diabetes, when camphor is administered, there takes place a excretion of considerable quantities of campho-glucuron-acid, without there being any decrease in the excretion of glucose. For 1 g. N there comes 1 g. glucuron acid (Rubner· Gesetze p. 393, foot-note). The nitrogen-free decomposition-products of protein in a phloridzin-diabetic dog should thus be 3.75 g. glucose + 1 g. glucuron-acid for 1 g. N, together 4.75, which approaches very nearly the figure 4.97 calculated by Rubner.

Apart from the question of the maximum sugar-formation from protein and from the question of sugar-formation from fat, it seems as if the determination of the quotient D/N can also be of importance in deciding the question whether sugar is consumed or not consumed in diabetes. A considerable decrease in the quotient D/N on diminished supply of protein or in hunger, where it previously has been a constant dimension during administration of large quantities of protein, most naturally seems to indicate that a constant consumption of sugar is always taking place. When the supply of protein is small, and the production of sugar does not exceed the requirements, the urine is free from sugar. If the sugar-production exceeds the requirements the excess is eliminated. As the nitrogen excreted should thus represent both consumed and excreted sugar, the quotient D/N will be small in the neighbourhood of the limit of consumption, but will rise rapidly with increasing supply of protein, until the ratio becomes constant, after which a further increase in the supply of protein should not produce any change.

According to the view which is here set forth, and which is based on the assumption that consumption of sugar takes place in diabetes, determination of the quotient D/N should have no application in investigations regarding the maximum sugar-formation from protein. As regards the question of sugar-formation from fat it seems that we may admit the existence of such formation, when D/N in the course of a not too short period exceeds the theoretically greatest possible value, and when at the same time it has been established by blood-sugar tests that there has not been any retention of sugar with subsequent profuse excretion, and that there is no retention of nitrogen either. Such results, however, have not hitherto been forthcoming.

3. Glucosuria after administration of various proteins.

The question whether the various proteins have different sugar-forming properties is of interest both from a theoretical and practical point of view. Earlier investigators of this question have carried out their investigations either upon patients suffering from diabetes mellitus, as was done by LÜTHJE (92), FALTA (93), FALTA and GIGON (94), MOHR (95), THERMANN (96), SCHUMANN-LECLERQ (97) and JUSTMANN (98), or else upon phloridzin-diabetic dogs, as was done by REILLY, NOLAN and LUSK (99), HALSEY (100), BENDIX (101), RÖHMER (102) and JANNEY (103). On pancreatic-diabetic dogs by LEHMANN (104), BERGER (105) and GEORG MÜLLER (106).

All these authors with the exception of HALSEY and JANNEY have found that *caseine* is the nitrogenous substance that produces most sugar, while meat comes second in order and ovalbumen generally third. HALSEY puts ovalbumen and JANNEY both gelatine and ovalbumen before caseine.

Since the chronic pancreatic diabetes offers great advantages in metabolic experiments stretching over a long period as compared with human diabetics and phloridzin-diabetic animals, we have carried out such investigations also on our pancreatic-diabetic dogs.

Without going more closely than I have already done into the technics and results of the experiments made by the investigators named, I shall here describe the experiments that have been carried out on one of our dogs.

The proteins which were experimented with were caseine, ovalbumen and gelatine. During a separate period, interposed between caseine and ovalbumen, experiments were also made with horsebeef.

Before the beginning of the tests the dog (dog I) was brought into nitrogen-equilibrium, and on a diet consisting of 300 g. horsebeef and 70 g. emulsified fat there was excreted about 32 g. glucose and 10 g. N. The dog was slightly acidotic with an ammonia-excretion of from 0.7 to 0.9 g. GERHARDT's reaction slightly positive (light burgundy-colour).

a. Caseine.

The dog was fed once every day. It got 200 g. lean horsebeef, 22 g. caseine and 70 g. fat. The caseine was from KAHLBAUM, prepared after HAMMERSTEN's method. KJELDAHL analyses were made of the meat and caseine. The caseine was emulsified together with the fat in 600 cm.^{3} water with the help of 2 cm.^{3} 10 % Na_2Co_3 and was administered by stomach-tube. The fat-caseine emulsion was given first, immediately afterwards it got the meat. The dog was allowed to drink water ad libitum. The experimental periods lasted three days, but for the caseine there was added an extra period of 2 days, the meat being by degrees completely replaced by caseine. The urine was collected in the course of 24 hours, and the excretion of sugar, nitrogen and ammonia was ascertained.

The result of the caseine tests is seen in Table 76.

Table 76.

Date	Sugar g.	N g.	D/N	NH_3	Nutriment
$^{13}/_8$	31.51	10.23	3.08	0.746	$^{12}/_8$ 200 g. horsebeef 70 g. fat 22 g. caseine } + 600 ccm. water 860 ccm. water.
$^{14}/_8$	33.40	10.31	3.23	0.823	$^{13}/_8$ 200 g. horsebeef 70 g. fat 22 g. caseine } + 600 ccm. water 1,040 ccm. water.
$^{15}/_8$	32.47	10.30	3.15	0.723	$^{14}/_8$ 200 g. horsebeef 70 g. fat 22 g. caseine } + 600 ccm. water 990 ccm. water.

The total excretion of sugar for the whole period is 97.38 g. The excretion of nitrogen is 30.84 g. The quotient D/N on the average for the whole period equals 3.22.

In the following days all the meat was gradually replaced by caseine. On the first day there was given 100 g. horsebeef, 44 g. caseine and 70 g. fat; on the second day no meat, 66 g. caseine and 70 g. fat. The excretion of sugar and nitrogen is constant (Table 77).

Table 77.

Date	Sugar g.	N g.	D/N	NH_3	Nutriment
16/8	32.76	10.98	2.98	0.829	15/8 100 g. horsebeef 44 g. caseine } + 600 ccm. water 70 g. fat } 1,050 ccm. water.
17/8	32.38	10.25	3.15	0.915	16/8 66 g. caseine } + 600 ccm. water 70 g. fat } 1,050 ccm. water.

b. Meat.

During a three-day period there was given every day 300 g. lean horsebeef and 70 g. emulsified fat. The technics of the experiment were otherwise as in the preceding experiment with caseine. The results are seen in Table 78.

Table 78.

Date	Sugar g.	N g.	D/N	NH_3	Nutriment
29/8	34.41	10.63	3.23	1.897	28/8 300 g. horsebeef 70 g. fat 1,170 ccm. water.
30/8	31.54	10.39	3.03	2.19	29/8 300 g. horsebeef 70 g. fat 1,100 ccm. water.
31/8	32.92	9.49	3.46	2.97	30/8 300 g. horsebeef 70 g. fat 1,015 ccm. water.

The sugar-excretion for the whole period is 98.87 g. and the nitrogen-secretion is 30.51 g. The average D/N for the whole period is 3.24.

c. Ovalbumen.

Immediately following the foregoing tests an experiment was made with ovalbumen (Merck). The technics were exactly the same as in the experiment with caseine. The dog gets every day 200 g. lean horsebeef, 22 g. ovalbumen and 70 g. emulsified fat (Table 79).

Table 79.

Date	Sugar g.	N g.	D/N	NH_3	Nutriment
1/9	35.01	10.19	3.43	1.927	31/8 200 g. horsebeef 22 g. ovalbumen } + 600 ccm. water 70 g. fat } 855 ccm. water.
2/9	37.92	11.26	3.36	2.042	1/9 200 g. horsebeef 22 g. ovalbumen } + 600 ccm. water 70 g. fat } 1,200 ccm. water.
3/9	24.26	7.25	3.34	1.813	2/9 200 g. horsebeef 22 g. ovalbumen } + 600 ccm. water 70 g. fat } 1,040 ccm. water.

The total excretion of sugar is 97.19 g., the nitrogen-excretion 28.70 g. The quotient D/N on the average for the whole period is 3.38.

d. Gelatine.

Technics as before. The dog is given daily 200 g. horsebeef, 22 g. gelatine and 70 g. fat. The gelatine was administered in the form of powder together with the fat-emulsion by means of stomach-tube (Table 80).

Table 80.

Date	Sugar g.	N g.	D/N	NH_3	Nutriment
6/9	35.32	9.75	3.62	2.031	5/9 200 g. horsebeef 22 g. gelatine } + 600 ccm. water 70 g. fat } 1,420 ccm. water.
7/9	35.42	9.50	3.80	2.264	6/9 200 g. horsebeef 22 g. gelatine } + 600 ccm. water 70 g. fat } 1,700 ccm. water.
8/9	36.24	11.30	3.20	2.411	7/9 200 g. horsebeef 22 g. gelatine } + 600 ccm. water 70 g. fat } 1,660 ccm. water.

The excretion of sugar for the whole period is 106.98 g., nitrogen-secretion 30.35 g. Average quotient D/N 3.52.

The safest starting-point for the comparison of the sugar-forming capacity of these different proteins in these experiments is the quotient D/N.

The quotient D/N in the experiment with caseine was 3.22.
» » » » » » » meat » 3.24.
» » » » » » » ovalbumen » 3.38.
» » » » » » » gelatine » 3.52.

If we have regard only to the quotient D/N we must place gelatine highest and caseine lowest with respect to sugar-forming capacity. There is, however, another circumstance, which cannot be left out of consideration in judging the results of these experiments, namely, that in the course of the period the experiments extended over, about 1 month, the animal's condition became worse. The NH_3-excretion has risen from 0.8 to over 2 g. daily, and the dog has decreased 1 kg. in weight, from 11.80 kg. to 10.80 kg. It cannot be left out of account that the increasing quotient D/N may be regarded as an indication of the aggravation of the animal's condition Perhaps the same increase would have taken place, if the proteins had been tested in the reverse order, gelatine first and caseine last. The difference between the quotient D/N in the first period, 3.22, and in the last period, 3.52, is moreover not so great that it alone, even if the animal's condition were not worse, could have been taken as deciding the question. All things considered, the results of the experiments seem rather to point to the conclusion that there is practically no difference in the sugar-forming capacity of the proteins investigated.

4. Glucosuria after administration of fat.

While the question of sugar-formation from protein may be regarded as finally solved, the question of sugar-formation from fat still remains undecided.

It is true, the literature records many observations of a high D/N quotient, for example, by BERNSTEIN, BOLAFFIO and WESTENRIJK (107), who found an increase in D/N (up to 10.6) in a diabetic on administration of fat in hunger, and by EPPINGER, RUDINGER and FALTA (108), who found a temporary increase to 7 in the quotient D/N after a copious supply of fat (with pancreatine) in the case of a pancreatic-diabetic dog. On the other hand, MOHR (130) on administration of fat and fatty acids (soaps) has obtained a reduction of the sugar-excretion in pancreatic diabetes. SCHMID (109) likewise observed in phloridzinpoisoned dogs a diminished excretion of nitrogen and sugar on feeding with fat-acids. In human diabetics BONDI & RUDINGER (110) have observed a distinct diminution in the sugar-excretion after the addition of fat to the previous diet, and another of their diabetics, who was free from sugar when fed with copious quantities of fat and smaller quantities of carbo-hydrates, got glucosuria again on the supply of fat being diminished, but was once again free from sugar, when the supply of fat was increased.

In spite of the fact that these experiments do not point to any formation of sugar from fat, yet the majority of authors are agreed that such formation is theoretically possible and even probable.

That glycerine, quantitatively a less important component of fat, is a sugar-former has been proved by KÜLZ (111) in human diabetics, by CREMER [(112) p. 889] in a phloridzin-poisoned dog, and by LÜTHJE (113) in a pancreatic-diabetic dog.

As regards the fat-acids, no objection can be brought from a chemical point of view against the possibility of sugar-formation from fat, even if experiments seem to speak against such formation. It is, however, not very likely that metabolic experiments will be able to decide this question. For, as PFLÜGER [(114) p. 328] and likewise VON NOORDEN [(42) p. 19] strongly emphasise, the metabolism of fat is not, like the metabolism of protein, determined by the supply, but by the body's consumption of energy. If more fat than is needed is supplied, it will be deposited, and if the supply is equal to the requirements, it will burn and will not be visible in any form. It is, however, possible that in the process of combustion part of the fat passes into glucose and that there exist metabolic anomalies through which this glucose becomes visible in the urine. GEELMUYDEN, especially, (154), (155), (156), (163), has defended the theory of the transition of ketones into glucose, relying on experiments made on phloridzin-poisoned animals. This assumption will, if it turns out to be correct, be of far-reaching importance for the understanding of the diabetic metabolism.

The experiments that have been made upon our dogs in order to contribute a little to the solution of this problem have given results similar to those of MOHR, BONDI and RUDINGER. One of the dogs (dog I) had not become free from sugar after 2 days' fasting, but only became so on the subsequent copious administration of fat during 2 days in quantities considerably exceeding its caloric requirements. After another day of fasting it again got glucosuria. The dog had considerable acidosis with ketonuria. The technics of the experiment were as follows: The fat, the melting-point of which was 25° C., was emulsified by means of 5 ccm. 10 % Na_2Co_3 + 300 ccm. water. It was administered by the stomach-tube. Water ad libitum. The fat was well absorbed. No diarrhoea.

The excretion of nitrogen diminishes with the increased supply of fat and the acidosis decreases. On the second fat-day the dog is free from sugar, but during the following fasting day it again gets glucosuria (Table 81). It seems that the result of the experiment must be interpreted to indicate that fat diminishes the glucosuria by sparing protein.

Table 81.

Date	Sugar g.	N g.	NH_3 g.	Nutriment
$^{18}/_{9}$	15.10	4.03	1.403	$^{17}/_{9}$ Fasting day Only water, drank 1,000 ccm.
$^{19}/_{9}$	4.45	4.11	1.135	$^{18}/_{9}$ Fasting day Drank 1,106 ccm. water.
$^{20}/_{9}$	1.69	3.34	0.077	$^{19}/_{9}$ 150 g. fat, emulsified, given by stomach-tube 1,160 ccm. water.
$^{21}/_{9}$	no sugar	2.42	0.798	$^{20}/_{9}$ 200 g. fat, emulsified, given by stomach-tube 630 ccm. water.
$^{22}/_{9}$	trace	2.20	0.585	$^{21}/_{9}$ Fasting day 560 ccm. water.
$^{23}/_{9}$	1.71	3.59	0.761	$^{22}/_{9}$ 100 g. horsebeef 120 g. fat 760 ccm. water.

The second dog (IV) had no acidosis and no acetonuria at the time the experiment was made. Technics as in the case of dog I.

Table 82.

Date	Sugar g.	N g.	NH_3 g.	Nutriment
$^{9}/_{9}$	8.99	4.78	0.419	$^{8}/_{9}$ 100 g. horsebeef 100 g. fat 550 ccm. water.
$^{13}/_{9}$	12.43	4.00	0.271	$^{12}/_{9}$ 100 g. horsebeef 100 g. fat 700 ccm. water.
$^{14}/_{9}$	no sugar	2.53	0.190	$^{13}/_{9}$ Fasting day Drank 400 ccm. water.
$^{15}/_{9}$	no sugar	2.46	0.195	$^{14}/_{9}$ 150 g. fat, emulsified 590 ccm. water.
$^{16}/_{9}$	no sugar	2.51	0.220	$^{15}/_{9}$ 150 g. fat, emulsified 900 ccm. water.
$^{17}/_{9}$	no sugar	3.11	0.426	$^{16}/_{9}$ 110 g. fat, emulsified 1,110 ccm. water.
$^{18}/_{9}$	6.28	3.80	0.323	$^{17}/_{9}$ 100 g. horsebeef 100 g. fat 550 ccm. water.
$^{19}/_{9}$	10.50	5.28	0.496	$^{18}/_{9}$ 100 g. horsebeef 100 g. fat 1,110 ccm. water.

The dog easily becomes free from sugar after a day's fasting. On administration of emulsified fat in quantities that exceed its caloric requirements, and which are well absorbed, no glucosuria appears. On a meat-diet it gets glucosuria again (Table 82).

The experiments are interesting from a practical point of view, but they solve none of the theoretical problems.

5. Metabolism of protein in hunger.

The excretion of nitrogen in normal animals when fasting calculated per kg. of body-weight is generally somewhat greater in smaller than in larger animals. Reckoned in percentage of the total metabolism the metabolism of protein in fasting animals in a good state of nutrition stands in a fairly constant ratio to the total metabolism. E. Voit [(115) p. 188, Table 12] has in normal dogs calculated the following values for the N-excretion per kg. body-weight in the course of 24 hours:

Dog, weight 28.6 kg. — 0.18 g. N.
» » 18.7 » — 0.20 g. N.
» » 7.2 » — 0.30 g. N.

Falta, Grote and Staehelin [loc. cit. (66) p. 214] have in normal dogs found the following corresponding values:

Dog, weight 23.7 kg. — N-excretion per kg. in 24 hours: 0.214 g.
» » 22.0 » — » » » » » » 0,202 g.

In a normal fasting human being E. Voit (loc. cit.) has reckoned an excretion of 0.20 g. N. per kg. in 24 hours, and in their control-individuals Benedict and Joslin [(62) p. 103] have made the following determinations (here re-calculated per 24 hours): 0.16, 0.14, 0.11, 0.13, 0.20, 0.18, 0.21, 0.18, 0.17, 0.13, 0.20, 0.11, 0.14, 0.14, average 0.16 g. N. per kg. in 24 hours.

After total extirpation of the pancreas Falta, Grote & Staehelin (loc. cit. p. 214) have in 2 dogs with a D/N quotient of 3.27 and 3.30 observed an increase in the nitrogen-excretion in hunger that is respectively 3 times and $4^{1}/_{2}$ times as great as in normal fasting animals, namely: from 0.214 g. N per kg. in 24 hours to 0.633 g., and from 0.202 g. N per kg. in 24 hours to 0.939 g. In one of Minkowski's dogs (16) with a

D/N equal to 2.66 Falta, Grote and Staehelin calculate the N-excretion per kg. in 24 hours at 0.75 g. In Kaufmann (90) they find the following values for the N-excretion per kg. in 24 hours in the case of totally depancreatised dogs:

D/N equal 3.11 — N in 24 hours per kg. body-weight: 0.90 g.
» » 2.88 — » » » » » » » 0.75 g.
» » 4.00 — » » » » » » » 0.93 g.
» » 2.93 — » » » » » » » 0.97 g.

Lüthje (116) has (according to the same authors) in a dog with total pancreatic-diabetes and with a D/N of 2.7 found an N-excretion per kg. in 24 hours equal to 0.8. In Almagia and Embden (83) they calculate the N-excretion per kg. in 24 hours at 1 g. in a pancreatic-diabetic dog with a D/N of 2.83, and in 2 dogs, both of which had a D/N of 2.85, Mohr (82) has observed 1.1 g. N per kg. in 24 hours.

Whilst the metabolism of protein is thus considerably augmented in dogs with total pancreas-diabetes, this is, according to Benedict and Joslin [(62) p. 103], in a much less degree the case in human diabetics. In individuals with grave diabetes they have found the following values (re-calculated here per 24 hours) for N-excretion per kg.: 0.20, 0.22, 0.15, 0.29, 0.16, 0.28, 0.14, 0.27, 0.13, 0.21, 0.18, 0.10, 0.23, 0.23, average for all determinations: 0.21 g., while, as already mentioned, in normal individuals they found an average N-excretion per kg. in 24 hours amounting to 0.16 g. The increase is thus very small, and in this non-increase of the metabolism of protein in hunger amongst human diabetics, although the D/N quotient is greater than 3.00, Falta (117), (71) perceives a very essential difference between diabetes mellitus and experimental pancreatic diabetes. It will be of interest to see how the metabolism of protein in hunger stands in the case of our partially depancreatised dogs, which, as already mentioned, had a high D/N quotient after a meat-diet.

Dog I.

First fasting-day 24 hours — 48 hours after the last meal, D/N equal 3.74:

N-excretion per kg. in 24 hours: 0.42 g.

Second fasting-day 48 hours — 72 hours after the last meal, D/N equal 1.82:

N-excretion per kg. in 24 hours: 0.43 g.

Fasting-day 24 hours — 48 hours after the last meal, fed exclusively with fat for 2 days, trace of glucose in urine:

N-excretion per kg. in 24 hours: 0.24 g.

Dog IV.

The dog had for some time had a D/N of between 3 and 4 after feeding on meat and fat. The day before the fasting-day it had after 100 g. horse-flesh and 100 g. fat a D/N of 3.10.

Fasting-day 24 hours — 48 hours after the last meal. No glucosuria:

N-excretion per kg. in 24 hours: 0.24 g.

Both dogs have therefore an increased nitrogen excretion in hunger (up to double the normal excretion), but it is far from reaching the same height as in totally depancreatised dogs, although the diabetic condition, judging by the D/N, is equally as grave as in the latter. And the value 0.24 g. N per kg. in 24 hours, which has been ascertained in both dogs, lies within the limits that have been established by BENEDICT & JOSLIN amongst human diabetics, and in this small increase in protein-metabolism in the case of these partially depancreatised dogs I am inclined to see a further point of similarity between the experimental chronic pancreatic-diabetes and diabetes mellitus. It seems not to be improbable that this similarity has come about through the diet, rich in carbohydrates and poor in meat, that the dogs have lived on all their life, and that perhaps, as already stated, a »transformation« of the metabolism has taken place.

6. The Metabolism of protein after administration of glucose.

After subcutaneous injection of glucose and saccharose into dogs and rabbits v. KÒSSA (118) has found an increase in the N-excretion. He also observed albuminuria and various other indications of the toxic effects of the sugar, such as muscular weakness and somnolence. SCOTT (162) has also after injection of glucose in quantities of from 5 to 7 g. per kg. observed an increase in the N-excretion in dogs. Underhill and Closson (21) have been able to confirm Scott's observations. After subcutaneous injection of glucose both the N-excretion and the P_2O_5-excretion increase. In contrast to Scott, however, they found that the ratio between the nitrogenous constituents of the urine was unaltered. In the case of rabbits, according to Heilner (121), (122), the situation is just the opposite, since he has observed in these animals a decrease in the N-excretion both after glucose and after injection of saccharose. Allen [(22) p. 208] found sometimes an increase in the N-excretion and sometimes an unaltered N-excretion after parenteral administration of glucose. Subcutaneous injections of more than 4 g. per kg. generally occasioned an increase. Generally speaking, he thinks he has observed that parenteral injections in the case of fasting animals do not spare protein.

In order to investigate how the administration of glucose per os affects the N-excretion in pancreatic diabetes the following experiment was carried out:

The dog (IV) was rendered free from sugar by restricting the amount of protein in the food. After 400 g. horsebeef and

Table 83.

Date	Quant. ccm.	Sugar g.	N g.	NH_3 g.	Nutriment
28/5	1,250	40.33	12.32	0.424	27/5 400 g. horsebeef 60 g. fat.
29/5	850	20.00	8.43	0.409	28/5 200 g. horsebeef 60 g. fat.
30/5	610	2.42	5.45	0.181	29/5 100 g. horsebeef 70 g. fat.
31/5	550	4.13	5.09	0.122	30/5 100 g. horsebeef 70 g. fat.
6/6	840	no sugar	3.77	0.172	5/6 100 g. horsebeef 70 g. fat 1,050 ccm. water.
7/6	1,160	no sugar	3.83	0.173	6/6 100 g. horsebeef 70 g. fat 1,200 ccm. water.
8/6	750	no sugar	3.60	0.176	7/6 100 g. horsebeef 70 g. fat 550 ccm. water.

60 g. emulsified fat the quotient D/N is over 3.00. After having got 100 g. horsebeef and 70 g. fat for 2 days the dog is free from sugar. During the following 3 days the dog gets the same diet and there is no glucosuria. This preliminary period is illustrated in Table 83.

The average N-excretion in the 3 sugar-free days is 3.73 g. In addition to this diet, which does not produce glucosuria, and in immediate succession to this period the dog now gets 20 g. glucose daily for 5 days. The results of the experiment are presented in Table 84.

Table 84.

Date	Quant. ccm.	Sugar g.	N g.	NH_3 g.	Nutriment
9/6	930	7.95	4.00	0.209	8/6 100 g. horsebeef 70 g. fat 20 g. glucose 170 g. water.
10/6	1,260	7.69	4.02	0.220	9/6 100 g. horsebeef 70 g. fat 20 g. glucose 1,060 g. water.
11/6	640	8.61	4.36	0.157	10/6 100 g. horsebeef 70 g. fat 20 g. glucose 495 g. water.
12/6	1,100	12.31	4.35	0.231	11/6 100 g. horsebeef 70 g. fat 20 g. glucose 810 g. water.
13/6	1,035	13.97	4.62	0.245	12/6 100 g. horsebeef 70 g. fat 20 g. glucose 1,050 g. water.

The N-excretion increases as soon as the glucose is given. The average N-excretion for the whole experiment is 4.25 g. N per 24 hours against 3.75 g. N in the preliminary period. The N-excretion increases evenly with the progress of the experiment. Some of the glucose given is assimilated. The glucosuria also increases as the experiment proceeds and may be interpreted as an aggravation of the condition on account of the »diabetic error« which the experiment represents.

N-equilibrium is not attained immediately after the conclusion of the experiment. The day after the glucose is withdrawn, the dog is free from sugar, but after the same quantity of meat and fat it excretes 4.35 g. N. Fourteen days later the N-excretion on the same diet is 3.45 g. The experiment is repeated once again on the same dog with the same result as in the first experiment (Table 85):

Table 85.

Date	Quant. ccm.	Sugar g.	N g.	NH_3 g.	Nutriment
6/7	870	no sugar	2.96	0.093	5/7 100 g. horsebeef 70 g. fat 750 g. water.
7/7	850	no sugar	2.97	0.087	6/7 100 g. horsebeef 70 g. fat 780 g. water.
8/7	900	no sugar	3.09	0.136	7/7 100 g. horsebeef 70 g. fat 800 g. water.
9/7	880	2.97	3.78	0.111	8/7 100 g. horsebeef 70 g. fat 20 g. glucose 950 g. water.
10/7	1,050	3.15	3.78	0.160	9/7 100 g. horsebeef 70 g. fat 20 g. glucose 850 g. water.

On the other dog (I) the experiment was made with 50 g. and 100 g. glucose without first rendering the dog free from sugar. After 300 g. horsebeef and 70 g. emulsified fat the dog excretes 33.90 g. glucose and 9.81 g. N (D/N equal 3.46). After 50 g. and 100 g. glucose the N-excretion rises to over 13 g. The glucose is excreted quantitatively (Table 86):

Table 86.

Date	Quant. ccm.	Sugar g.	N g.	NH_3 g.	Nutriment
9/9	1,050	33.90	9.81	2.334	8/9 300 g. horsebeef 70 g. fat 1,000 g. water.
10/9	1,980	82.68	13.32	2.492	9/9 300 g. horsebeef 70 g. fat 50 g. glucose 1,900 g. water.
11/9	2,975	135.49	13.01	3.143	10/9 300 g. horsebeef 70 g. fat 100 g. glucose 2,800 g. water,
12/9	2,450	41.78	13.23	2.618	11/9 300 g. horsebeef 70 g. fat 2,450 g. water.

It appears from these experiments that when administered per os to pancreatic-diabetic dogs glucose has not, as normally, a protein-sparing effect, but that the protein-metabolism increases as the result of such an oral administration of glucose.

7. Feeding with pancreas.

A very prominent place in SANDMEYER's work (8) is taken up by his experiments with pancreas-feeding. He observed that when fresh ox-pancreas was given together with horse-flesh or beef to his pancreatic-diabetic dogs the glucosuria increased, or glucosuria could be produced by the addition of fresh pancreas to a meat diet, which alone did not produce glucosuria. From his tables (p. 82 and p. 80) the following extracts are taken:

Total sugar-excretion in 4 days after	800 g. horse-flesh:	8.02 g. glucose
» » » 4 » »	800 g. horse-flesh + 200 g. raw ox-pancreas:	62.66 g. »
» » » 5 » »	1,200 g. horse-flesh:	17.05 g. »
» » » 4 » »	1,200 g. horse-flesh + 200 g. raw ox-pancreas:	102.10 g. »

After boiled ox-pancreas he observed (as far as is shown in the tables on p. 78 and p. 81) no increase in glucosuria:

Total sugar-excretion in	4 days	after 1,000 g. horse-flesh + 200 g. raw pancreas per day:	14.64 g. glucose
» »	» 4 »	» 1,000 g. horse-flesh + 200 g. boiled pancreas per day:	6.65 g. »
» »	» 1 day	» 1,200 g. boiled pancreas per day:	3.00 g. »
» »	» 1 »	» 1,200 g. raw pancreas per day:	54.68 g. »

Sandmeyer himself believes that this effect of the raw pancreas is due to better digestion and utilisation of the protein on account of the enzymes contained in the raw pancreas.

Pflüger (123) was able to confirm Sandmeyer's observations, as also was Lüthje (124). Reach (126), (127) proved by means of partially depancreatised dogs that raw meat produces glucosuria, whilst boiled meat has not the same effect, and he thinks, that raw meat has a toxic action. According to this view, the glucosuria after raw pancreas should be due not to better digestion and absorption, but to the raw state of the meat.

On one of our dogs (IV) an experiment was made with boiled and raw pancreas, the results of which are given here.

Table 87.

Date	Quant. ccm.	Sugar g.	N g.	D/N	NH_3 g.	Blood-sugar %	Nutriment
12/10	1,450	10.37	5.83	1.77	1.31	0.23	11/10 100 g. boiled pancreas 100 g. horsebeef 120 g. fat.
13/10	1,800	8.88	5.22	1.70	1.31	0.23	12/10 100 g. boiled pancreas 100 g. horsebeef 120 g. fat.
14/10	1,420	5.24	5.89	0.80	1.31	0.23	13/10 100 g. boiled pancreas 100 g. horsebeef 120 g. fat.
15/10	1,210	5.35	5.92	0.90	1.37	0.23	14/10 200 g. horsebeef 120 g. fat.
16/10	1,020	6.65	5.10	1.30	1.26	0.23	15/10 200 g. horsebeef 120 g. fat.
17/10	1,070	6.85	5.22	1.31	1.23	0.24	16/10 200 g. horsebeef 120 g. fat.

Experiment with boiled ox-pancreas.

Immediately after its removal from the animal the pancreas was placed in a freezing-mixture and frozen stiff. The frozen glands were boiled immediately after coming to the laboratory. The dog received daily for 3 days 100 g. boiled ox-pancreas, 100 g. horse-flesh and 120 g. emulsified fat. After this followed a period with 200 g. horsebeef and 120 g. emulsified fat. The results are shown in Table 87.

It is seen that the sugar-excretion decreases from 10.37 g. the first day to 5.24 g. the third day, whilst the nitrogen-excretion is unchanged. The quotient D/N declines from 1.77 to 0.80. The concentration of blood-sugar is 0.23 % all three days. The NH_3-excretion is likewise unaltered. In the after-period with horsebeef there is an insignificant increase in the sugar-excretion.

In immediate succession to the after-period with meat-diet an experiment was made with raw ox-pancreas.

Experiment with raw ox-pancreas.

The dog got the same quantities of raw pancreas, horsebeef and fat as in the experiment with boiled pancreas. The tech-

Table 88.

Date	Quant. ccm.	Sugar g.	N g.	D/N	NH_3 g.	Blood-sugar %	Nutriment
$^{18}/_{10}$	1,290	8.71	5.94	1.46	0.99	0.24	$^{17}/_{10}$ 100 g. raw pancreas 100 g. horsebeef 120 g. fat.
$^{19}/_{10}$	1,380	7.23	5.49	1.31	0.96	0.23	$^{18}/_{10}$ 100 g. raw pancreas 100 g. horsebeef 120 g. fat.
$^{20}/_{10}$	1,200	11.36	6.01	1.87	1.55	0.23	$^{19}/_{10}$ 100 g. raw pancreas 100 g. horsebeef 120 g. fat.
$^{21}/_{10}$	1,300	10.61	5.44	1.95	1.39	0.22	$^{20}/_{10}$ 200 g. horsebeef 120 g. fat.
$^{22}/_{10}$	1,390	15.24	5.44	2.88	1.57	0.22	$^{21}/_{10}$ 200 g. horsebeef 120 g. fat.
$^{23}/_{10}$	1,900	14.52	6.16	2.35	1.75	0.24	$^{22}/_{10}$ 200 g. horsebeef 120 g. fat.

nics were in every respect the same. The period with pancreas-feeding lasted 3 days, after which, as in the former experiment, there followed an after-period with horse-flesh. The results are given in Table 88.

The sugar-excretion rose from 8.71 g. the first day to 11.36 the third day. The N-excretion is unchanged, likewise the concentration of blood-sugar. The quotient D/N rose to 1.87. In the after-period the sugar-excretion rose the second day to 15.24 g., whilst the N-excretion was not increased The D/N was 2.88.

The experiment with raw pancreas has given the same results as those previously obtained by SANDMEYER, PFLÜGER and LÜTHJE, namely: that raw pancreas augments the glucosuria. The effects of boiled pancreas seem to tend in the opposite direction, namely: a diminution of the glucosuria. From SANDMEYER's tables it seems to be evident that he also has obtained such an effect from boiled pancreas, although this view is not directly expressed.

The observations and experiments recorded in this section may briefly summed up as follows:

The clinical picture of a manifest chronic diabetes of respectively 8 and 13 months' duration has been described in the case of 2 dogs. A slight, a medium grave and a grave form of glucosuria were observed. There existed polyuria and polydipsis, gradual emaciation and polyphagia, ketonuria and acidosis, albuminuria and cataract.

In the chapter on metabolism the investigations that have hitherto been carried out regarding the total metabolism both in diabetes mellitus in human beings and in the experimental pancreatic diabetes have been exhaustively discussed. An attempt has been made to give an explanation of the genesis of the increased metabolism, which according to the more recent investigation may with more or less certainty be said to exist in grave diabetes.

The value of determinations of the respiratory quotient has been discussed with the object of deciding whether or not a consumption of sugar takes place in diabetes. The conclusion is come to that this question cannot be solved in this way, and it is therefore regarded as being a still unsolved problem.

Determinations of the quotient D/N have been made 179 times altogether. In both of the partially depancreatised dogs there was found *on the average* a slightly higher quotient D/N than in MINKOWSKI's dogs with total pancreatic diabetes, namely: 3.00 and 3.10. There were often observed values between 3.5 and 4, occasionally over 4.

Investigations regarding glucosuria after feeding with various proteins have yielded the experimental result that we may place gelatine highest and after it ovalbumen, meat and caseine with respect to the sugar-forming capacity of these substances. But as we cannot disregard the fact that the patient's condition has grown worse in the course of the tests, the experiments must on the whole be taken as indicating that there is, practically speaking, no difference in the sugar-forming capacity of the proteins investigated.

Investigations regarding the effect of the administration of fat on the glucosuria do not point to any sugar-formation from fat, since a dog that was not free from sugar after 2 days' fasting became free from sugar on the following day after being fed with fat and afterwards got glucosuria again after a subsequent fasting-day. The experiments are, however, only of interest from a practical point of view and solve none of the theoretical problems.

The metabolism of protein in hunger was found to be increased in the case of both dogs, but it is far from reaching the same height as in totally depancreatised dogs, although the quotient D/N is just as high as in the case of the latter.

Examinations of the excretion of nitrogen after administration of glucose have shown that the protein-metabolism (N-excretion) increases in pancreatic-diabetic dogs as a result of administration of glucose per os.

Experiments with pancreas-feeding have confirmed the results obtained by earlier investigators. Raw pancreas augments the glucosuria, boiled pancreas seems to diminish it.

The relationship of hyperglycemia to ventricular secretion has been examined. Feeding-tests with protein-fat show an increase in the blood-sugar amongst the diabetic dogs. The increase coincides with the termination of the ventricular digestion and the evacuation of the ventricle and has reached its highest point before the absorption is completed. — Bouillon administered per os causes a great increase in hyperglycemia in a pancreatic-diabetic dog, a distinct increase in a depancreatised but not yet diabetic dog, but no increase in a healthy dog. Experiments with administration of water and with regard to psychic secretion reveal a distinct increase in the hyperglycemia amongst diabetic animals.

Post-mortem Findings.

After total extirpation v. Mehring and Minkowski found the liver strongly infiltrated with fat, so that it contained up to 30 or 40 % of fat. Of the pancreas tissue they found no trace. They make no record of pathological changes in the other organs.

In dogs with chronic diabetes after partial extirpation of the pancreas Sandmeyer found microscopic traces of apparently normal pancreas tissue. The other organs were normal, the liver was not infiltrated with fat, the kidneys normal. Thiroloix and Jacob [loc. cit. (35) p. 378] have found that in chronic pancreas-diabetes the liver may be enlarged, infiltrated with fat and sclerotic. All the other organs were normal. Allen and Mallory [(22) p. 898—985] have observed no changes in any other organs except the pancreas amongst diabetic animals. The thyreoideae, kidneys and genital glands were always found to be normal in chronic pancreatic diabetes (loc. cit. p. 977). In diabetic animals they always found degenerative changes in the islands of Langerhans, such as a smaller number of cells in the island, deficiency of the cytoplasma in many of the persisting cells, pycnotic degeneration of the nuclei and occasionally naked nuclei.

In this chapter shall be recorded the results of dissection in the case of the 4 partially depancreatised dogs.

In the microscopic examination the following technics were employed:

In the case of dogs I and VI, fixation in kaliumbichromat-formol according to Kopsch and in picricacid-aceticacid-formol according to Bouin.

For dogs II and III fixation in formalin.

The usual colour-method was hæmatoxylin-eosin. As special colour-methods there were also employed VAN GIESON's picro-fuchsin colouring, ferro-hæmatoxylin and Sudan.

All the remnants of pancreas were examined by the use of seriate cuts.

Dog I.

The dog is 20 months old. 17 months have elapsed since the operation, manifest diabetes has been existent for 9 months.

Dissection $^{18}/_{3}$ *1918.*

The head.

The bones of the cranium are brittle and thin.

Meninges slightly congested.

The brain of normal consistence and appearance.

The hypophysis of the size of a grain of shot, 4 mm. in diameter.

Neck.

Thyreoidea dextra weighs 1.2 g., sinistra 1.1 g.

Parathyreoidea sup. d. lies loose in the capsule, is about 5 mm. long, 4 mm. broad and 2 mm. thick. The lower glandule lies in the thyreoideal substance, but shines through the capsule. It is about 4 mm. long and 2 mm. broad.

Parathyreoidea sup. s. likewies lies in the capsule and is of the same size as on the right side. The same is the case with the lower glandule. About the *tongue*, *pharynx*, *esophagus* and the large *vessels* of the neck there is nothing to remark.

Chest.

The ribs are brittle.

Pericardium smooth and reflectant, no fluid in the pericardial cavity.

The heart is large and flabby. The valves normal.

Pleura smooth and reflectant, no exudation.

The lungs contain air, are soft and crepitant.

The abdomen.

Omentum, almost without fat, only slight traces of fat along the vessels. No adhesions between the omentum and the intestine.

Peritoneum, smooth and reflectant all over, no exudation.

The stomach, somewhat distended, contains a little mucous, clear liquid.

Duodenum is found in its entire length adhering fast to the lower edge of the liver.

Jejunum. About 40 cm. below the pylorus there is found an intussusception. Above the seat of the intussusception the jejunum and duodenum are distended and filled with gas and liquid. From the seat of the intussusception downwards the intestine and the mesentery are greatly congested. There is, however, no gangrene or discoloration otherwise.

Pancreas.

On that spot on the duodenum which corresponds to the caput pancreatis there is found a thick, hard, sclerotic remnant of the pancreas, 4 cm. long, 1 cm. broad and $^3/_4$ cm. thick. Weight 3.2 g. A finger's breadth above this spot there is another small, hard piece of the pancreas, about the size of a bean, weight 0.5 g. Otherwise no remnants of pancreas tissue or aberrant parts of the pancreas are to be found.

The liver is large, weight 468 g. Upper surface smooth and reflectant. Consistency soft. On the incision surface are seen fairly conspicuous yellowish-white stripes and patches in the red-brown tissue.

The kidneys are large. The right kidney weighs 79 g., the left 78.5 g. Consistency soft, surface smooth, colour pale. The capsule easy to remove. On the incision surface the colour is pale all over. In the corticalis there are some blurred markings. Distinct boundary between the cortex and the medulla. The cortex bulges and is raised a little higher than the margin of the medullar-cone.

The adrenal glands are found to be isolated on both sides. The size is that of a large bean. The left one weighs 0.9 g., the right one 0.8 g.

The milt is pale, atrophic; weight 5.0 g.

Microscopic examination.

Pancreas. The largest piece shows considerable hypertrophy of the connective tisssue, which at several points completely displaces the pancreas tissue. No LANGERHANS cells. The smaller piece of the pancreas is surrounded by a thick capsule of connective tissue. From this a great number of strips of connective tissue proceed into the parenchyma and displace the latter. The cells of the acini are in a condition of active secretion. No LANGERHANS cells.

Thyreoidea. The epithelium around the different follicles is greatly proliferated so that in several places it appears in plural layers, at certain spots even the lumen is wanting. Between the follicles there is only a scanty amount of colloid substance. On the other hand, a colloid like substance is seen extending in long columns through the lymph-fissures between some of the alveoli.

Parathyreoidea: shows no distinct alterations.

Hypophysis: no distinct alterations.

Testis shows some infiltration of fat in the interstitial tissue.

The liver is greatly infiltrated with fat.

The kidneys. The epithelium of the renal canals is seen to be desquamated. In most of the epithelium-cells cavities are seen. In Sudan-preparation the epithelium in many of the renal canals, especially the right, is seen to be full of particles of fat.

Adrenal glands. In the cortex, especially in zona glomerulosa, the cells are seen to be filled with numerous drops of fat, considerably larger than the normal lipoid grains. Some of the drops of fat coalesce and form large cavities. In Sudan-preparation the cells in the cortex are seen to be filled with drops of fat. The medulla-substance is unchanged.

Dog II.

The dog is 2 years old. 20 months have elapsed since the operation. Clinical diagnosis: Decreased tolerance for carbohydrates, but no manifest diabetes. The dog was killed with chloroform.

Dissection $^{14}/_{6}$ *1918.*

The head.

Cranium, normal.

In the meninges and brain nothing to remark.

Hypophysis, 4 mm. in diameter.

Neck.

Thyreoidea sinistra weighs 4 g., dextra also 4 g.

Both parathyreoideae sup. are loose in the capsule, are 5 mm. × 4 mm. × 3 mm. Parathyreoideae inf. lie in the thyreoideal substance.

Tongue, *pharynx* and *esophagus* are normal.

Chest.

In the heart and lungs nothing to remark.

Abdomen.

Omentum: fatty.

Peritoneum: smooth and reflectant.

Stomach and intestines normal.

Pancreas. On the duodenum at the place of operation there is a remnant of pancreas the size of a bean, and just in the neighbourhood of this a smaller piece, the size of a grain of shot. The remnants are hard, sclerotic and together weigh 0.45 g. At the curvatura major about 5 cm. above the pylorus, just up to the junction-point of the omentum and on the under side of the latter, there is found, firmly fixed with strong adhesions, a very sclerotic remnant of the pancreas (cauda), 1.5 cm. long and 1 cm. broad, weighing 0.8 g. It is completely surrounded by omental fat. In this remnant there still remains a linen thread from the operation. After the piece of pancreas has been cut away, web-like filaments are seen in the ventricle-wall, spreading out like a star from the point of adhesion.

On one side of the duodenum, beside the operation-scar and completely isolated from it, there is found, subserously situated in the duodenal wall itself, a piece of pancreas-tissue the size of half a pea, not sclerotic, of the consistence of normal pancreas-tissue.

The adrenals lie isolated on both sides, the left one weighs 1.2 g., the right one 1.0 g.

The ovaries are the size of a bean.

The liver weighs 355 g. Surface smooth and reflectant. Consistence normal. On the incision surface the tissue of the liver is seen to be red-brown all through.

The kidneys are of normal size; the right kidney weighs 33 g., the left one 34 g. The surface is smooth, the capsule easy to loosen. On the incision surface the markings in the corticalis are distinctly seen, likewise the boundary between the medulla and the cortex.

The milt is large, weight 33 g.

Microscopic examination.

Pancreas.

In one of the sclerotic pancreas-remnants from the duodenum there are seen in the centre groups of acini. In the surrounding connective tissue are seen several groups of cells of the acini.

In the other sclerotic pancreas-remnant there are seen in the connective tissue groups of acini, partly moulded by the proliferating connective tissue.

The non-sclerotic pancreas-remnant from the duodenum consists of normal pancreas acini in an active state of secretion and very few islands of LANGERHANS.

The caudal pancreas-remnant. Deposited in the connective tissue are seen groups of epitheloid cells lying close together and resembling LANGERHANS cells. There is seen no trace of acini. Some of the cell-groups are of the same size and appearance as normal islands of LANGERHANS, but most of them are considerably larger. On seriate cuts through the whole preparation the same cell-masses are seen everywhere disseminated through the connective tissue, which in its proliferation seems to be on the point of compressing the hypertrophied epitheloid cell-masses.

Thyreoidea: Strong proliferation of the epithelium of the gland, so that the follicles in most places are obliterated. Only scanty colloid substance.

Parathyreoideae and hypophysis normal.

The adrenals, the liver, kidneys and ovaries show no alterations.

The liver contains glycogen.

Dog III.

The dog is $17^1/_2$ months old. 12 months have elapsed since the operation. Clinical diagnosis: Decreased tolerance for carbohydrates, but no manifest diabetes. The dog was killed with chloroform.

Dissection $^{16}/_7$ *1918.*

Head.

The cranium, meninges and brain normal.

Hypophysis somewhat larger than in the previous dissections, 5 mm. in diameter.

Neck and chest.

Both thyreoideae large.

Weight of right thyreoidea with both parathyreoideae 3 g.
» » left » » » » 3 g.

In heart and lungs normal conditions.

Abdomen.

Peritoneum smooth and reflectant. No adhesions to the abdominal wound.

Omentum, fatty, evenly spread over the upper part of the intestines. On the right side are seen a number of adhesions between the peritoneum parietale and the duodenum, as well as between the duodenum and the colon ascendens. Between the lower surface of the liver and the duodenum there are exceedingly strong adhesions. There is here felt a hard lump, which cannot be loosened from the liver without lacerating the tissue of the liver. The duodenum is carefully cut away from the liver at this point. The lump situated on the outside of the duodenum, at the place of operation, is 3.5 by 2.5 by 2 cm. Otherwise no trace of pancreas tissue can be found.

The liver weighs 293 g., surface smooth, consistency normal, incision surface brownish-red all over. The bile-ducts intact.

The milt weighs 23 g. Surface smooth, consistency normal.

The adrenal glands of normal size, weighing 1 g. each.

The kidneys. Both kidneys have on their surface a number of web-like filaments. On incision it is seen that the cortex-substance at these spots has disappeared and is completely converted into cicatrice-tissue. The right kidney weighs 27.5 g. and the left one 27 g.

The ovaries are of the size of a bean, of normal appearance.

Microscopic examination.

Pancreas. The preparation consists mainly of granulation-tissue. On the duodenum, around the excretory ducts of the pancreas there is a remnant of pancreas the size of a nut, consisting of acini and islands of LANGERHANS. These latter are considerably more numerous than normally. In the surrounding granulation-tissue epithelium-cells are disseminated, arranged sometimes in groups, sometimes in filaments. In most places they are changed in form, so that it is difficult to decide whether they come from acini or from islands.

Thyreoidea. Extreme proliferation of the gland-epithelium, as in the case of the former dogs.

Parathyreoidea and hypophysis normal.

Adrenal glands and ovaries show no alterations.

The liver and kidneys normal.

Dog IV.

The dog is 23 months old. $13^1/_2$ months have elapsed since the operation. There has been manifest diabetes for over 13 months.

Dessection $^1/_6$ *1918.*

Head.

The bones of the cranium thin and brittle. In the meninges and brain nothing to remark.

Hypophysis, the size of a grain of shot, 3.5 by 3.5 mm.

Neck.

Thyreoidea dextra. Weight including both parathyreoideae 0.65 g. Length 14 mm., breadth 8 mm., thickness 5 mm. The loose parathyreoidea dextra is 3 by 2 by 2 mm. The intracapsular one is of corresponding size.

Thyreoidea sinistra was removed together with one parathyreoidea (the intracapsular). Length 15 mm., breadth 8 mm., thickness 4 mm., weight 0.60 g. The visible part of the parathyreoidea 5 by 4 mm.

As to tongue, pharynx, esophagus and the large vessels there is nothing to remark.

Chest.

Pericardium normal.

Heart, pale, flabby. The musculature pale, yellowish in colour.

Adipose deposit quite absent.

Pleura smooth and reflectant.

Pulmonary tissue normal.

Abdomen.

Between the umbilicus and the sternum, in the cicatrice from the operation, there is a hernia giving room for the insertion of 4 fingers.

On opening up the peritoneal cavity the intestines are seen in the normal position.

Peritoneum is smooth and reflectant all over, except that part of the peritoneum parietale that corresponds to the hernia, at which place for the space covered by a child's hand the peritoneum is thickened and somewhat uneven, with adhesions from the omentum.

Omentum is nearly destitute of fat and is spread evenly over the upper part of the intestines except at the spot mentioned, where it adheres to the abdominal wall. On attempting to lift up the omentum from the underlying intestines, adhesions to the latter were discovered, especially in the upper portion up towards the duodenum, where the intestines are adherent over a very large area. Also on the lower surface of the liver there are adhesions of the omentum as well as of the duodenum, which, however, can be loosened without laceration of the liver-tissue. There are also very slight adhesions between the upper surface of the liver and the diaphragm.

The stomach is large and seems to be somewhat distended, is full of undigested food.

The intestines are of normal appearance.

Pancreas. The remnant around the excretory ducts was carefully cut away. Length 15 mm., breadth 11 mm., thickness 6 mm. Weight 1.5 g. The tissue is completely hard, sclerotic, squeaks under the knife.

The liver, large, weight 530 g. Surface smooth and reflectant, showing slight impression of ribs. Consistency somewhat soft. On the incision surface are seen yellowish-white patches and stripes in the brownish-red tissue.

The bile-ducts are intact.

The kidneys are somewhat enlarged. The right kidney weighs 58 g., the left kidney weighs 58.5 g. Surface smooth, of a yellowish colour. The capsule easily loosened, consistency soft. On the incision surface the substance of the cortex is seen to be swollen, the markings blurred, the colour very yellow.

The adrenal glands lie isolated. Weight, the right one 0.8 g., the left 0.7 g.

Ovaries: Weight together 0.7 g., small, atrophied.

The milt, pale, atrophied. Length 8 cm., breadth 1 to 2 cm., thickness 0.1 to 0.5 cm. Weight 4.5 g.

Microscopic examination.

Pancreas. Considerable hypertrophy of the connective tissue with shrivelling and necrosis of the glandular acini. No LANGERHANS cells.

Thyreoidea, extreme proliferation of the epithelium.

Parathyreoidea and hypophysis show no perceptible alterations.

Adrenal glands, great infiltration of fat in the cortex-substance, as in dog I. The medullary substance somewhat diminished.

Ovaries, normal.

The liver, infiltrated with fat, but not so much as in the case of dog I. Contains 9.59 % fat and only a trace of glycogen.

The kidneys present the same picture of fatty degeneration as in the first dog.

Summary review.

The object of the investigations has been in the first place by means of systematically executed tolerance-tests to examine how the glucosuria arises and develops after partial extirpation of the pancreas in dogs of different ages, and in which an attempt was made to render the metabolism more like that of human beings by means of a diet rich in carbo-hydrates and free from meat, and by varying the method of operation to examine the question whether removal of different parts of the pancreas is of significance.

In the second place the object has been to investigate from a metabolic and clinical standpoint the chronic diabetes that occurs, paying special attention to the points that are of interest for comparison of this condition with the genuine human diabetes mellitus.

Finally one has endeavoured by means of exact anatomical examination of the material obtained from dissection to investigate the anatomical basis for the internal function of the pancreas, and to seek for clues to enable us to form a judgment regarding the influence of the endocrine organs on the diabetic state.

In 3 puppies (Dogs I, II and III) there were removed respectively 8/9ths, 7/8ths and 6/7ths of the pancreas. In dogs I and III the duodenal portion around the excretory ducts was left behind, in dog II the caudal portion. Immediately after the operation and during the whole time the investigations lasted (9, 19 and 12 months) examinations were made regarding the glucose-tolerance, and control-tests were carried out on normal animals of the same litter, which lived under the same conditions as the operated animals. Dogs I and II had in the first 2 or 3 months after the operation a decreased tolerance for glucose. The tolerance increased, however, according as the animals grew up, both absolutely and relatively in proportion to the dogs' weight, and finally after about 3 months reached such a height in the case of dog I, that glucosuria could not be produced with quantities of 120 g. glucose (11 g. per kg.), and in the case of dog II glucosuria could not be produced 8 months after the operation with 90 g. glucose (9.3 g. per kg.). After an interval of 6 and of 8 months respectively, during which the tolerance was normal, it again began to decline in these 2 dogs, and in one of them there now developed a diabetic condition. The other was killed for purposes of examination at this stage of development. (19 months after the operation.) Dog III, from which 6/7ths of the pancreas had been removed, showed for over 9 months after the operation no decreased tolerance for glucose. In spite of the absence of so large a part of the pancreas, the dog tolerated 100 g. glucose (23 g. per kg.) without getting glucosuria. Not until 10 months after the operation did it get glucosuria after administration of 100 g. glucose. From this time on the tolerance declined, so that 1 year after the operation it got glucosuria after 50 g. glucose (5.6 g. per kg.).

From a full-grown dog, 9 months old (dog IV), 8/9ths of the pancreas were removed. The duodenal portion was left behind. The operation was thus essentially the same as in the case of dog I. This dog got glucosuria on ordinary diet immediately after the operation.

From the operation till the appearance of the spontaneous glucosuria there thus elapsed in the cases of these 4 operated dogs a time of very different duration. For dog I 9 months, for dog II 19 months, for dog III 12 months (until the tolerance declined), while in the case of dog IV glucosuria appeared immediately after the operation. In dogs I and IV there developed a chronic diabetes which ended with death after 8 and 13 months respectively. The other 2 dogs were killed immediately before the transition to chronic diabetes out of regard for the interest attaching to an examination of the remnant of the pancreas and the other endocrine organs.

As regards *the development of the diabetic state* enlightenment is obtained from the feeding-tests with glucose, starch and meat during the period between the operation and the time when the diabetic condition was manifest: Decreased tolerance for *glucose* is the earliest indication of a change in the carbohydrate-metabolism after partial extirpation of the pancreas. In succession to this period with decreased glucose-tolerance there gradually develops a condition which is characterised by the fact that also large quantities of *starch* produce glucosuria, but in which glucosuria does not occur after feeding with protein and fat alone. This period steadily merges into a condition in which *large quantities of protein* (300 g. meat) produce glucosuria, but in which the glucosuria vanishes on restriction of the quantity of protein (100 g. meat). The glucosuria then develops further and is manifest also after *small quantities of protein* (100 g. meat), and finally it becomes difficult, or altogether impossible, to get the glucosuria to disappear even after *fasting-days.*

With respect to *the relationship between glycemia and glucosuria* it has been proved that the percentage of blood-sugar (which normally is from 0.08 % to 0.09 %) can rise to 0.17 % without glucosuria occurring. The lowest observed concentration of blood-sugar producing glucosuria is 0.19 % both in normal and in operated animals. *The total quantity of glucose excreted* depends not only on *the degree of hyperglycemia* but also on its *duration for values over 0.19 %.* This last factor seems to be the most important. *The concentration of glucose* in the urine is proportional to the concentration of blood-sugar.

The further investigations have had especially in view the relationship between the experimental chronic diabetes and the genuine diabetes mellitus.

With the object of rendering the metabolism of the animals experimented on as like as possible to that of human beings these dogs, from the moment they came to the laboratory as

6 weeks old puppies, were fed only on bread and milk, never on meat.

The chronic diabetes that developed in two of the operated dogs (I and IV), of which the former was operated when a puppy and the latter when full-grown, lasted 8 and 13 months respectively after the glucosuria had become manifest even on a meat-diet. In the case of the dog that was operated on when a puppy, the transition from a normal carbo-hydrate-metabolism to a manifest diabetes was rapid. (3 or 4 weeks.) In both dogs the condition was allowed to develop itself freely. The resemblance to genuine diabetes mellitus was striking. The glucosuria was accompanied by polyuria and polydipsia. There was observed a gradual transition of the glucosuria from a lighter to a medium-grave and graver form. This transition was accompanied by emaciation and polyphagia. Later on there appeared ketonuria and acidosis with an excretion of up to 2.38 g. total-aceton per day (animal's weight: 9.60 kg.) and 1.81 g. total-aceton per day (animal's weight: 8.90 kg.), and an ammonia-figure (HASSELBALCH) of 20 to 30. Both dogs got albuminuria a short time after the acidosis arose. In both dogs cataract occurred, in one of them (dog I, operated when a puppy) as early as a couple of months after the glucosuria was manifest, in the other (IV) not until the glucosuria had lasted a whole year.

The object of the metabolic tests that were carried out on these dogs with chronic diabetes was in the first place to investigate the importance of determinations of the quotient D/N in the solution of the question of the maximum sugar-formation from protein and of the question whether sugar-formation from fat could be proved to exist. while at the same time it would be of interest to see how this matter stands in the case of these dogs, which in many points showed so great a resemblance to human diabetics.

Determinations of the quotient D/N have been made altogether 179 times. In the two partially depancreatised dogs I and IV there was found after feeding exclusively with meat a slightly higher quotient D N than in MINKOWSKI's dogs with total pancreatic diabetes, namely: 3.00 and 3.10. There were often observed values between 3.5 and 4, occasionally over 4. As appears from the previous discussion of this question and according to the views there set forth, based upon the assumption that there is a consumption of sugar in diabetes, determinations of the quotient D/N should not be applicable in investigations regarding the maximum sugar-formation from protein.

Investigations regarding the glucosuria after feeding with various proteins yielded the experimental result that gelatine has the greatest sugar-forming capacity, after it coming ovalbumen and meat, whilst caseine has the least capacity. As appears from the discussion that follows the recording of the experiments, since we cannot disregard the fact that the dog's condition has become worse in the course of the tests, these experiments must be taken as indicating that there is practically no difference in the sugar-forming capacity of the proteins examined.

Investigations regarding the effect on the glucosuria of administration of fat did not point to any sugar-formation from fat, since a dog that was not free from sugar after 2 fasting-days, became free from sugar the next day after administration of fat and then got glucosuria again after a subsequent fasting-day. The experiments, however, have only a practical clinical interest and solve none of the theoretical problems.

The metabolism of protein in hunger was found to be increased in the case of both dogs, but was far from reaching the same degree as in totally depancreatised animals, although the diabetic condition, judging by the quotient D/N, was just as grave as in the case of the latter.

Investigations regarding metabolism of protein after administration of glucose have shown that glucose has not here, as normally, an protein-sparing effect, but that the nitrogen-excretion increases in pancreatic-diabetic dogs as the result of administration of glucose per os.

Experiments with pancreas-feeding have confirmed the results arrived at by earlier investigators. Raw pancreas increases the glucosuria. Boiled pancreas seems to diminish it.

Observations have been made which point to the conclusion that the hyperglycemia stands in a definite relationship to ventricular secretion. Bouillon per os occasions a great increase in hyperglycemia in a pancreatic-diabetic dog, a distinct increase in a depancreatised but not yet diabetic dog, but no increase in a healthy dog. Experiments with administration of water and with respect to psychic secretion of gastric juice reveal a distinct increase in the hyperglycemia in diabetic animals.

The anatomical investigations have embraced a complete macroscopic and microscopic examination of all organs. Their special object, however, was to examine the anatomical basis for the internal function of the pancreas and by examination of the endocrine organs to seek for clues that might help us in forming a judgment regarding the relationship of these organs to the diabetic condition.

In the remnants of the pancreas in the diabetic dogs I and IV islands of Langerhans *were not found, but only externally secreting pancreas-tissue, in one of them (I) in an active state. In the non-diabetic dogs, II and III, islands of* Langerhans *were found, and in one of them, (II), there was observed a considerable hyperplasia of these islands and only very small remnants of externally secreting pancreas-tissue.*

The thyreoidea was found hypertrophied in all the depancreatised animals, both the diabetic and the non-diabetic.

The parathyreoidea and hypophysis were found unchanged.

The cortex of the adrenal glands in the diabetic dogs I and IV contained more fat than usual, the medulla was unaltered. In the operated non-diabetic dogs II and III the adrenal glands were normal.

In the testis the interstitial tissue was infiltrated with fat (Dog I), and the ovaries were macroscopically atrophied in the diabetic dog IV, unaltered in the non-diabetic dogs II and III.

The liver in the diabetic dogs, I and IV, was infiltrated with fat and showed only a trace of glycogen. The kidneys were also infiltrated with fat, the milt atrophied. In the operated non-diabetic dogs II and III the liver, kidneys and milt were normal.

Concluding remarks.

When the results here recorded are considered in relation to the object in view, it will be seen that we have succeeded in producing a condition which both from a clinical and from a metabolic standpoint has many points of similarity with the genuine human diabetes mellitus, while at the same time we have been able to get an insight into the manner in which this condition develops out of a normal carbo-hydrate metabolism. The anatomical examinations have rendered it possible to form a judgment regarding the circumstances that have been partly the cause and partly the result of this condition.

In the following pages the reflections which these results suggest will be discussed. They will purposely be treated separately from the standpoints of physiology, pathologic physiology and anatomy.

1. Physiology.

If the results of the investigations are considered from an endocrinological standpoint, assuming that the metabolic anomaly itself, i. e.: the disturbance of the carbo-hydrate metabolism and the conditions arising immediately out of this disturbance, are directly occasioned by the restriction of the internal function of the pancreas, the results will then be found to be in extensive agreement with the ordinary features in the development of corresponding conditions after partial extirpation of other endocrine organs. Thus, a comparison with the results of partial parathyreoidectomy will be very interesting and striking. If 3 gl. parath. are removed, there arises a mild form of tetanus, which, however, disappears after a short time and is succeeded by an interval during which the animal seems to be perfectly well. After a period of from several months up to 1 year the animal again gets tetanus and dies in convulsions. The removal of 2 glandules, as a rule, does not occasion tetanus, while the removal of 4 glandules produces an acute tetanus, which results in death in a few days. [TANBERG (131)].

The condition that arose in the dogs operated on when puppies (I and II) are completely analogous with the condition after removal of 3 gl. parath.: immediately after the operation symptoms of insufficiency, then a latent period and finally a rapid collapse.

That dog IV got glucosuria immediately is perhaps due to the fact that it was operated on when full-grown. The part left behind was of the same size and the same portion of the pancreas as in the dog first operated on. But relatively, in proportion to the size of the animal the portion left behind would, of course, be smaller. It is, however, more probable that the result is due to the fact that the young animal has a greater power of regeneration than the full-grown animal, and to judge by what was discovered on dissection it seems as if the remnant of the pancreas in the puppy (dog I) has increased in size after the operation, and this increase in size may well be supposed in this case to have taken place simultaneously with the growth of the other organs and does not need to be due to any compensatory hypertrophy. In the case of the other puppies, in which no macroscopic hypertrophy of the pancreas-remnant was found on dissection, it may be admitted that the insufficiency may have been compensated for by an increased function in the young animals, or that the internally secreting elements may have been hypertrophied (as in dog II), without its being just necessary for the whole organ to have increased in size.

The results yielded by the alimentary tests in the case of the 3 animals operated on when puppies (I, II and III) may be taken as pointing to an insufficiency of the internal function of the pancreas, and it seems as if the tolerance-tests with glucose can be applied as function-tests with regard to this function. The deficiency of pancreas must, however, be very great before the tolerance-test yields a positive result in the form of glucosuria. To judge from the experiments here recorded, the deficiency must be greater than 6/7ths before glucosuria occurs. As in all other endocrine organs, there is here a large »reserve».

Regarding the mode and field of action of the internal pancreas-secretion the investigations regarding blood-sugar seem to give some enlightenment. It was proved that a concentration of blood-sugar of over 0.19 % was followed by glucosuria. For the extent of the glucosuria (the total quantity of glucose excreted) the duration of the blood-sugar concentrations of over 0.19 % was of greater significance than very high concentrations of blood-sugar of shorter duration. The disturbance in the assimilation of carbo-hydrates found expression not only in the high concentration of blood-sugar necessary to produce glucosuria, but also in the duration of that concentration and in the fact that smaller quantities of glucose at that stage caused a greater concentration of blood-sugar and of longer duration than larger quantities at an earlier point of time. In all the blood-sugar tests we got the distinct impression that it was the *velocity* with which the sugar disappeared from the blood that had the most important influence on the result with respect to the question of glucosuria or no glucosuria.

It seems quite natural after these results to assign to the internal secretion of the pancreas properties that have influence on the *velocity* with which the sugar administered per os disappears from the blood-courses. Without more exactly defining this internal secretion, it seems as though we must agree that it has a *catalytic* effect.

After DE FILIPPI's investigations regarding the alimentary glucosuria in dogs with ECK's fistula (28) it seems, as if the liver has little influence in the production of glucosuria. The dogs with ECK's fistula that were operated on did not get alimentary glucosuria more easily than normal animals. KLEINER (132) found that intravenously injected glucose disappears just as quickly from the blood in the case of animals that have undergone nephrectomy as in normal animals. Also in the dead animals intravenously injected glucose quickly disappeared from the blood-courses, and the phenomenon was independent of the abdominal organs. In these experiments the carbo-hydrates in the muscles increased both in the living and in the dead animals, and in most cases polysaccharides were formed. BANG [(37) p. 61 and p. 82] supposes the existence of another carbo-hydrate deposit in the organism besides glycogen, and ALLEN [(22) p. 383] puts forward the hypothesis that the internal secretion of the pancreas is a colloid amboceptor, the union of which with the glucose prevents the glucose from going over into the urine. The greater part, however, fixes itself upon the cells and participates in the building up of the colloidal protoplasm. Diabetes is defined by ALLEN as the absence of this amboceptor. Both BANG and ALLEN put forward their hypotheses as explaining why glucosuria does not so easily occur on oral or other administration of glucose in normal individuals.

After the results that have been here recorded concerning the blood-sugar it seems unnecessary to have recourse to unknown deposits of carbohydrates in order to find an explanation for the disappearance of the sugar, and it likewise seems unnecessary to explain the occurrence of the glucosuria in diabetics by assuming a decreased combustion or a defective glycolysis. Both phenomena can be explained as the result of alterations in the *velocity* with which the normal conversion of glucose to glycogen takes place. The chemical processes may be assumed to be qualitatively unaltered both in normal individuals and in those with decreased tolerance, but the *velocity of reaction* may be supposed to be altered, where the glucose-tolerance is reduced, so that the result of the process from a quantitative point of view becomes different. Until the presence of another carbo-hydrate is proved it is to be assumed that the substance into which the glucose is normally so quickly converted is glycogen. For this function the liver is from a quantitative standpoint specially adapted, and the liver also through the vena porta receives the internal secretion of the pancreas sooner than any other organ, but glycogen-formation takes place also in the muscles and probably to quite as great an extent there as in the liver. In this place it may be mentioned that VAN SLYKE and MEYER (133) have observed a similar state of affairs as in the case of glucose also in the case of the amino-acids. Injected amino-acids disappear quickly from the blood and can be absorbed directly by the tissues without having passed through the liver and without preceding deaminisation. Even though the liver is especially differentiated for the deaminisation of amino-acids and for the formation of urea, yet it does not stand alone in the carrying out of this process.

The slow formation of glycogen both in the liver and in the muscles, which is assumed to be the result of an insufficiency of the internal function of the pancreas, must in the diabetic organism result in a hyperglycemia. When this becomes chronic, the protoplasmic effects of the hyperglycemia appear in the form of increased cellular metabolism [CSERNA and KELEMEN (74)] and afterwards of the other consequences of this augmented metabolism (see p. 90). The fact that the hyperglycemia can vary in intensity explains why in diabetes we may find the metabolism sometimes higher and sometimes lower. [BENEDICT & JOSLIN (62)], [ALLEN & DU BOIS (67)].

With regard to the quotient D/N, sugar-formation from protein and fat, and the effects of administration of glucose the reader is referred to the discussion of these points under the respective headings.

2. Pathological physiology.

The chronic diabetes that developed in dogs I and IV, is very interesting from a metabolic-pathological point of view. Several new observations have been made, which place the condition that can develop after partial extirpation of the pancreas in a somewhat different relation both to the earlier known forms of experimental pancreatic diabetes and to diabetes mellitus. Earlier investigators, such as BRUGSCH [loc. cit. (47)] BRUGSCH & BAMBERG [loc. cit. (48)] and especially FALTA (134) find such great differences between the metabolism in pancreatic-diabetic dogs and in human diabetics that they cannot bring themselves to recognise in the genuine diabetes mellitus any pancreatic diabetes. BRUGSCH and BAMBERG find in the absence of acidosis in dogs with pancreatic-diabetes the most essential difference between this and diabetes mellitus. FALTA, as already mentioned, regards the state of the quotient D/N (which in dogs with total pancreatic diabetes lies around 2.8 and up to 3, whilst in diabetes mellitus it can considerably exceed 3 for many weeks together), the enormous excretion of nitrogen in hunger (and great excretion of salt) and especially the absence of ketonuria in pancreatic-diabetic dogs as constituting the most essential differences between the experimental pancreatic diabetes and the genuine diabetes mellitus.

These differences are not distinguishable in our dogs. On the contrary, there is a close agreement. *The quotient D/N*, in spite of the fact that the pancreas had been only partially extirpated, has for weeks together been *considerably higher than was previously observed* in any dog with total pancreatic diabetes and has several times exceeded the values that can be found in diabetes mellitus. *The excretion of nitrogen in hunger* is, in spite of this high quotient D/N, *not very much increased, and the ketonuria is quite considerable* with an excretion of over 2 g. total aceton per day in a dog weighing about 9 kg., which corresponds to 16 or 18 g. in a human adult. To this must be added *a strong sinistral rotation* of the fermented urine and *considerable* NH_3*-excretion* in the urine together with *a high ammonia-figure.*

The observations are also interesting in other respects. The *glucosuria*, *albuminuria* and *cataract* developed in a manner quite corresponding to what is seen in human diabetics.

SANDMEYER's dogs had not ketonuria. GERHARDT's reaction was negative during the whole course of the disease, and LIEBEN's reaction was only now and then faintly positive, which SANDMEYER records as a trace or a minimal trace. In our two dogs, I and IV, ferric-chloride reaction gave during a fairly long period a dark burgundy-colour, often quite black (in the protocols marked with + + and + + +), and the iodoform test yielded in the un-distilled urine a cloudy, milk-like result with considerable sediment. As already mentioned, acidosis and ketonuria have also been observed in pancreatic-diabetic dogs by ALLEN (22), (72) and ALLARD (49), by ALLARD only in totally depancreatised animals, by ALLEN also in partially depancreatised. As to the dog's mode of life before the operation we are given no information.

The differences and the resemblances in metabolism between the various forms of experimental pancreatic diabetes and diabetes mellitus will be most clearly seen when the characteristics that distinguish the separate forms are set forth in tabular form. I shall here confine myself to the points of importance which FALTA (loc. cit. p. 410 and 411) has brought out in illustration of the contrast between total pancreatic diabetes and diabetes mellitus.

Total pancreatic diabetes.	Diabetes after partial extirpation of the pancreas. (SANDMEYER's diabetes.)	Diabetes after partial extirpation of the pancreas and ›transformation‹ of the metabolism.	Chronic diabetes mellitus in human beings.
The quotient D/N when the diabetes is fully developed is 2.8. (MINKOWSKI.)	The quotient D/N when the diabetic condition was at its highest point was 2.0.	The quotient D/N on the average was over 3.0 and often values between 3.5 and 4 (now and then over 4).	The quotient D/N often over 3 (up to 3.65, Lusk).
Enormous rise in the metabolism of protein in hunger (3 and 4$^1/_2$ times as large as normally) and in excretion of salt.	Metabolism of protein in hunger not investigated.	Metabolism of protein in hunger somewhat increased (from quite slightly up to double).	Metabolism of protein in hunger inconsiderably increased.
Most often no ketonuria.	No ketonuria.	Considerable ketonuria.	Considerable ketonuria.

If we are to seek for the reason why these dogs have presented this new picture so divergent from the earlier known conditions, I think it is to be found in the animals' mode of life. As already stated, they did not get any meat. From the moment they were taken from the mother, as 6 weeks old puppies, they received only bread and milk. Also after the operation the dogs that were operated on when puppies got only bread and milk right up to the time when the glucosuria appeared, while the dog that was operated on when full-grown got nothing else but bread and milk before the operation. By means of the diet rich in carbo-hydrates the metabolism of these carnivorous animals was presumably »transformed», that is to say, the metabolic processes which may be assumed to be qualitatively alike for all mammals, are supposed to have been altered quantitatively, so that processes that formerly proceeded to a smaller extent or more slowly now proceed to a larger extent and more rapidly (which means that the velocity with which the processes proceed is the decisive factor from a quantitative standpoint), — or else processes that formerly proceeded more rapidly and to a larger extent have now in the new mode of life become superfluous and proceed on a smaller scale, a view which is in agreement with an explanation previously put forward by GEELMUYDEN (153). As mentioned in the introduction, dogs do not normally get acidosis in hunger. But if they are put on a carbo-hydrate diet for a long time and afterwards allowed to fast, they get acidosis and ketonuria [VON NOORDEN (42) p. 201]. And the Eskimos, as is well known, thrive excellently on a diet of meat and fat exclusively, wherefore we may assume that their metabolism also has been »transformed» to resemble that of the carnivori.

Such a »transformation» of the metabolism may be supposed to have taken place in these dogs. They have thereby acquired a metabolism very similar to that of human beings, and this new »normal» metabolism, on the operation being performed, reacts in such a way that there develops a condition such as has been described, and which both from a clinical and from a metabolic-pathological standpoint resembles in a high degree diabetes mellitus.

As constituting one point of difference between the experimental pancreatic diabetes and diabetes mellitus FALTA emphasizes also the circumstance that on administration of protein to dogs with total pancreatic diabetes there arises an incongruence of the nitrogen-curve and the sugar-curve, since the apex of the sugar-curve comes long before that of the nitrogen-curve, whilst in diabetes mellitus the curves for the sugar and for the nitrogen run congruently. This matter has not been directly investigated in the case of these dogs. But after the investigations regarding hyperglycemia after feeding with protein this incongruence can easily be explained. The fact is that the blood-sugar curve after protein-feeding in pancreatic-diabetic dogs does not follow the course of the absorption. As soon as the sour contents of the stomach come down into the duodenum, the concentration of blood-sugar begins to increase (exactly the same after administration of protein and fat as after administration of water and bouillon and as on psychic secretion of gastric juice). It may be assumed that the sour contents of the stomach have, when absorbed, an action on the liver, and thus it is the absence of the alkaline pancreatic-juice that is the cause of the incongruence between the curves for sugar and nitrogen and not any difference in the metabolism. To this absence of pancreatic-juice in the intestines there may, moreover, in my opinion, be assigned an essential significance with respect to the progress of the experimental pancreatic diabetes. It is clear that when there constantly takes place such an injurious action on the liver, as is the case in pancreatic-diabetic dogs after the diabetic condition has arisen, there is in the case of these dogs an aggravating factor, which is not present in diabetes mellitus. The comparatively rapid progress of the chronic pancreatic diabetes in dogs, as compared with the progress of diabetes mellitus, can perhaps be explained in this manner.

A similar injurious action on the liver, resulting from the absorption of the sour contents of the intestine, can also be observed in partially depancreatised dogs, where the diabetic condition has not yet arisen. There comes a distinct increase of the blood-sugar, but of short duration and of minor extent and not accompanied by glucosuria. It seems that this state of affairs can only be explained by assuming that the internal function of the pancreas is maintained, and, in accordance with the explanation already given of the mechanism connected with the occurrence of hyperglycemia and glucosuria, it is probable that here also it is a question of velocity. Both in the diabetic and in the non-diabetic dog the action on the liver is the same, and in both cases hyperglycemia occurs, but the velocity with which the increased quantity of blood-sugar again disappears is decisive both for the further progress of the glycemia and for the resulting glucosuria.

When the points of resemblance between this new form of pancreatic diabetes and diabetes mellitus have been so strongly emphasised in the foregoing pages, the point of difference here mentioned must also be clearly pointed out. The circumstance is most probably of essential significance in accounting for the comparatively rapid progress of the chronic pancreatic diabetes.

The difference in the manner of death most also be emphasised. None of the dogs died in coma. Death in coma has, however, as mentioned, been observed among dogs with pancreatic diabetes by Allard (49).

From a clinical standpoint the slight, medium-grave and grave forms of glucosuria, albuminuria and cataract, which were observed in both dogs, are of interest, but demand no further discussion.

3. Anatomy.

The observations made on dissection will be discussed with a view to the following points:

1. The anatomical basis for the internal function of the pancreas.
2. Anatomical indications for or against the connection of the other endocrine organs with the diabetic condition.

The investigators who regard an affection of the pancreas as the anatomical basis for diabetes are not all agreed as to whether that affection has its seat in the acini of the glandular parenchyma itself (acinous theory) or in the cells of Langerhans (insular theory) or both in the acini and in the islands (acino-insular theory).

The »acinous theory» has been propounded by v. Hansemann (142), (143), but has met with little support. The »insular theory» has the most adherents. The most important spokesmen for this theory are Weichselbaum & Stangl (134), (135), Opie (136), Cecil (138), Laguesse (139) and Weichselbaum (140), (151), all of whom dwell upon the qualitative pathological-anatomical alterations of the islands of LANGERHANS in diabetes mellitus (sclerosis, hæmorrhagia, hyalin-degeneration, hydropic degeneration, leucocyte-infiltration), whilst HEIBERG (141) especially emphasizes the quantitative alterations, i. e., changes in the number of the islands of LANGERHANS. The »acino-insular» theory has found supporters in REITMANN (144), HERXHEIMER (145) and KARAKASCHEFF (146).

The *experiments* that have been carried out by the different investigators support the »insular theory». Thus, LAGUESSE has excised the ductus pancreaticus in rabbits and after 2, 3 and 4 years respectively, during which time the rabbits showed no sign of glucosuria, the animals were killed. The externally secreting portion of the pancreas had entirely disappeared, but the islands of LANGERHANS remained. KIRKBRIDE (149) attained the same results. ALLEN & MALLORY's experiments (22) also seem rather to favour the insular theory. MINKOWSKI (150) has in 1908 had the following experience: From 2 dogs the pancreas was removed and the duodenal portion subcutaneously transplanted, so that the external secretion continued unhindered. One dog got grave diabetes. In this dog the pancreatic juice was abundantly secreted the whole time from the subcutaneous remnant, which on microscopic examination proved to consist only of acini. The other dog got a very slight diabetes, the pancreatic juice was more sparingly secreted from the considerably diminished remnant of the pancreas, which on microscopic examination proved to contain normal LANGERHANS cell-groups in a sclerotic tissue.

The experiments recorded in this work, taken together with the findings made on dissection, support in the strongest manner the »insular theory». In the remnants of the pancreas in the diabetic dogs I and IV islands of LANGERHANS were *not* found, but on the other hand acini, which in one of the dogs (I) at any rate were in an actively secreting state. In the non-diabetic dogs II and III there were found only small remnants of acini, while in both dogs were found piles of cells resembling the cells in normal islands of LANGERHANS, and in one dog (II) there was considerable hyperplasia of these cells.

The experimental data for the »insular theory», which we have in the quoted works of LAGUESSE, KIRKBRIDE, ALLEN and MALLORY and MINKOWSKI, are thus supported and complemented by the observations that have been made in this work, since on the one side we have diabetics with remnants of pancreas having no islands of LANGERHANS, but with acini, on the other side non-diabetics having islands of LANGERHANS, some of which are considerably hypertrophied, and only insignificant remnants of acini. The experimental proofs in favour of the »insular theory» have thereby become so numerous that we are entitled to believe that the anatomical basis for the internal secretion of the pancreas is to be found in the islands of LANGERHANS.

Here the question arises as to what importance these investigations have for the understanding of the pathogenesis of human diabetes.

Without wishing to regard these experimental facts as proving that diabetes mellitus is due to a diseased condition of the islands of LANGERHANS, one shall here mention that WEICHSELBAUM (140) has investigated 183 cases of diabetes and found in all of them undoubted pathological-anatomical alterations of the islands of LANGERHANS. The alterations comprised atrophy, sclerosis, hæmorrhagia, hyalin-degeneration, hydropic degeneration and fatty degeneration. And CECIL (138) has found anatomical lesions of the pancreas in more than 7/8ths of the 90 cases of diabetes examined. In such cases, where diabetes was associated with lesions of the pancreas, the islands of LANGERHANS showed constant pathological changes: sclerosis, hyalin-degeneration, leucocyte-infiltration. Similar observations were made by WEICHSELBAUM and STANGL (134), (135), OPIE (136) and LAGUESSE (139) whilst HEIBERG (141), (141a) as already mentioned, specially emphasizes changes in the number of the islands of LANGERHANS, while at the same time admitting the possibility of an initial stage with qualitative alterations. Thus he has seen WEICHSELBAUM's hydropic degeneration lead to a complete disappearance of islands. These pathological-anatomical observations, taken together with the experimental facts, speak strongly in favour of the opinion that the cause of diabetes is to be found in a disease of the pancreas and especially of the islands of LANGERHANS.

We must, however, here mention what the opponents of this pancreas-theory have to adduce. In the first place it is objected, that on dissection there can be found deep-working changes in the pancreas without diabetes. This objection is in accordance with our experimental results, which have shown that at least 6/7ths of the pancreas must be removed before there occurs the slightest disturbance of the carbo-hydrate metabolism. Greater experimental deficiencies, however, produce diabetes, and with extensive necrosis of the pancreas in human beings diabetes has repeatedly been observed, for instance, quite recently by CARO and WINKLER (152). The other objection is this, that we often meet with diabetes without any changes in the pancreas. The exact investigations that have been carried out by WEICHSELBAUM [loc. cit. (140)] and by CECIL [loc. cit. (138)] permit us, however, to suppose that a close examination of the islands with employment of suitable methodics will in general lead to acknowledgment of the existence of pathological changes. The small amount of tissue in the islands in comparison with the whole gland (HEIBERG estimates the total weight of the island-tissue at 2 or 3 g.) is no doubt a principal reason for the non-observation of pathological changes in this tissue.

The last question to be discussed is whether the findings made on dissection have yielded proofs for or against the assumption of an influence on the part of the other endocrine organs on the diabetic condition. The demonstration of the influence of extracts from certain organs on the carbo-hydrate metabolism between the endocrine organs has given birth to the hypothesis of a polyglandular origin for the diabetic condition. According to this view, of which the principal supporters are EPPINGER, FALTA and RUDINGER (157), the pancreas and parathyreoidea are organs restrictive of metabolism, of which the hormones restrain the sympathetic and stimulate the para-sympathetic nerve-system. The chromaffine system, thyreoidea and hypophysis are organs promoting metabolism, of which the hormones stimulate the sympathetic and restrain the para-sympathetic nerve-system. Between themselves the organs constituting these two groups mutually assist each other, but each organ in the one group acts restrictively upon the activity of any organ whatsoever in the other group.

Adrenal injections mobilise carbo-hydrates and fat, the effect being increased by administration of thyreoideal substance and being weakened by extirpation of the thyreoidea. Thyreoideal substance increases the metabolism of protein, fat and salt, and it can produce glucosuria. Injection of hypophysis-extract can also cause glucosuria, and extirpation of the parathyreoidea may bring about a decrease in the tolerance for glucose. According to this hypothesis the pancreas acts as the great restrictive apparatus.

In accordance with this hypothesis one should expect, when this great restrictive apparatus, the pancreas, is eliminated, to find anatomical indications of hyperfunction of the antagonistic organs. Such an observation would in the strongest manner support this polyglandular hypothesis, and we should then be forced to assign to these endocrine organs an essential importance with regard to the diabetic condition and to assume that there is an active co-operation on the part of these organs in the genesis of this condition.

The microscopical investigations that have been carried out in this work yield *no* indications in support of the polyglandular hypothesis.

In the adrenal glands the medulla presents no signs of hyperfunction.

The thyreoidea was found to be greatly hypertrophied both in diabetics and in non-diabetics. The hypertrophy cannot therefore be specific for diabetes. Such hypertrophy has also been observed by SWEET and ELLIS (158) after removal of the external function of the pancreas in extirpations of the duodenal portion.

The parathyreoidea and hypophysis show no certain changes.

The findings in dissection combined with the experimental results seem to assign to a primary insufficiency of pancreas the most important role in the genesis of all diabetic phenomena. The fact that these conditions can be aggravated or alleviated by action of the other endocrine organs ought, it would seem, to be regarded in the same way as we regard the action of pharmacological substances, and need not necessarily involve a supposition of an active »reciprocal action» between these organs and the pancreas.

After having for many years put the other endocrine organs in the foreground, one will probably have to return to the pancreas, and to regard this organ as the seat of the causative lesion.

And perhaps before very long the view will be generally accepted, which was first propounded by BOUCHARDAT (164), LANCÉREAUX (165) and LAPIERRE (166), and which, before ever the experimental pancreatic diabetes was known, was so briefly and concisely expressed by BAUMEL (167): »La cause du diabète n'est pas élastique, comme on l'a prétendu; elle est toujours due à une lésion, parfois macroscopique, souvent microscopique, d'autrefois simplement dynamique (action nerveuse ou circulatoire) du pancréas.»

Protocols.

Partially depancreatised dogs.

Dog I.

Deerhound, male, age $3^1/_2$ months. Weight 3.70 kg.

Partial pancreatectomy $^{16}/_{10}$ 1916. Removal of the horizontal part and the extremity of the vertical part of pancreas. — Parts removed had a length of 15 cm. and weighed 12 g. Remnant $1^1/_2$ cm., communicating with both ducts. — Vessels intact.

Date	Weight kg.	Urine						Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D [1]	Glucose g. polarim.	Glucose g. BANG.	
$^{15}/_{10}$	3.70	130	—	—	0			$^{14}/_{10}$ 150 g. dogbiscuits.
$^{16}/_{10}$	3.70	340	—	—	0			$^{15}/_{10}$ 190 g. dogbiscuits. $^{16}/_{10}$ partial pancreatectomy.
$^{17}/_{10}$	3.60	160	—	—	— 0.3			$^{16}/_{10}$ no food. $^{17}/_{10}$ no vomiting. Lively.
$^{18}/_{10}$	3.57	280	—	—	— 0.1			$^{17}/_{10}$ 100 g. dogbiscuits.
$^{19}/_{10}$	3.53	435	+	+	+ 0.1	0.41	1.08	$^{18}/_{10}$ 750 ccm. skim-milk.
$^{20}/_{10}$	3.55	690	+	+	+ 1.0	6.53	7.52	$^{19}/_{10}$ 1000 ccm. skim-milk.
$^{21}/_{10}$	3.60	60	—	—	— 0.2			$^{20}/_{10}$ 150 g. dogbiscuits.
$^{22}/_{10}$	3.65	150	—	—	— 0.1			$^{21}/_{10}$ 150 g. dogbiscuits.
$^{23}/_{10}$	3.60	130	—	—	— 0.1			$^{22}/_{10}$ 150 g. dogbiscuits.
$^{24}/_{10}$	3.60	85	—	—	— 0.15			$^{23}/_{10}$ 150 g. dogbiscuits.
$^{25}/_{10}$	3.60	430	—	—	— 0.15			$^{24}/_{10}$ 5 g. glucose with stomach-tube, 250 g. minced horse-meat.

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[1] The values of α correspond to a tube of 20 cms length.

Date	Weight kg.	Urine						Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	Glucose g. BANG	
26/10	3.65	430	—	—	+ 0.2			25/10 7 g. glucose, 250 g. minced horse-meat.
27/10	3.70	310	—	—	+ 0.1			26/10 10 g. glucose, 250 g. minced horse-meat.
28/10	3.75							Vomiting yesterday after having eaten the collodium-bandage.
29/10	3.80	230	+	+	+ 0.2	0.87	1.19	28/10 20 g. glucose, 250 g. minced horse-meat.
30/10	3.85	370	+	+	+ 0.6	4.37	5.21	29/10 25 g. glucose, 250 g. minced horse-meat.
								30/10 Dog with-drawn from cage. Gets hereafter every day 200 g. bread and 500 ccm. skim-milk.
10/11	5.05	375	—	—	— 0.2			9/11 27 g. glucose, 300 g. minced horse-meat.
11/11	5.05	485	+	+	+ 0.7	6.3	6.49	10/11 32.5 g. glucose, 300 g. minced horse meat.
12/11	4.97	630	—	—	— 0.1			11/11 400 g. horse meat.
13/11	5.05	450	—	—	— 0.15			12/11 400 g. horse-meat.
22/11	5.70	820	+	+	+ 0.1	1.55	2.05	21/11 39 g. glucose, 390 g. minced horse-meat.
23/11	5.75	685	+	+	+ 0.15	1.95	2.09	22/11 39 g. glucose, 390 g. minced horse-meat.
24/11	5.85	440	—	—	— 0.2			23/11 500 g. horse-meat.
3/12	6.90	960	—	—	— 0.2			2/12 45.5 g. glucose, 500 g. minced horse-meat.
4/12	7.00	915	—	—	— 0.2			3/12 45.5 g. glucose, 500 g. minced horse-meat.
5/12	7.17	1005	+	+	+ 0.2	1.89	2.66	4/12 60 g. glucose, 500 g. minced horse-meat.

Date	Weight kg.	Urine						Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	Glucose g. BANG	
6/12	7.30	790	+	+	+ 0.3	2.24	2.65	5/12 60 g. glucose, 500 g. minced horse-meat.
7/12	7.40	980	+	+	+ 0.25	2.50	7.22	6/12 80 g. glucose, 500 g. minced horse-meat.
8/12	7.50	870	+	+	+ 0.17	6.59	7.09	7/12 80 g. glucose, 500 g. minced horse-meat.
9/12	7.75	915	+	+	+ 1.7	14.82	13.17	8/12 100 g. glucose, 500 g. minced horse-meat. With-drawn from the cage.
17/1 17	10.60	960	—	—	— 0.1			16/1 100 g. glucose, 600 g. minced horse-meat.
18/1	11.05	980	—	—	— 0.1			17/1 120 g. glucose, 600 g. minced horse-meat.
13/3	15.00	240	—	—	— 0.15			12/3 750 ccm. skim-milk, 300 g. bread.
20/3	15.45	1330	—	—	0			19/3 80 g. glucose, 650 g. minced horse-meat.
21/3	15.60	1720	+	+	0	trace	0.79	20/3 100 g. glucose, 650 g. minced horse-meat.
22/3	15.70	1530	+	+	+ 0.55	7.95	7.95	21/3 130 g. glucose, 650 g. minced horse-meat.
23/3	15.70	1420	+	+	+ 0.4	5.20	5.37	22/3 115 g. gjucose, 650 g. minced horse-meat
12/4	16.80	1270	+	+	+ 0.15	1.70	3.05	11/4 740 ccm. skim-milk, 450 g. bread.
13/4	16.80	1400	+	+	+ 0.94	13.16	12.60	12/4 1000 ccm. skim-milk, 450 g. bread.
17/4	17.20	1345	+	+	+ 2.9	36.90	38.50	16/4 1000 ccm. skim-milk, 450 g. bread.
21/4	16.80	1465	—	—	— 0.1			20/4 80 g. glucose, 700 g. minced horse-meat.
27/4	16.55	1020	—	—	— 0.2			26/4 500 g. bread.
28/4	16.70	745	—	—	— 0.2			27/4 500 g. bread.

Date	Weight kg.	Urine.						Remarks.
		Quant. ccm.	Reduction-tests	Phenyl-hydrazin-test	α_D	Glucose g. polarim.	Glucose g. BANG	
29/4	16.65	860	+	+	+ 0.25			28/4 500 g. bread.
1/5	16.75	1795	—	—	— 0.6	10.23	10.95	30/4 100 g. glucose, 700 g. minced horse-meat.
3/5	16.60	690	+	+	+ 2.0	13.07	14.21	2/5 100 g. glucose, 700 g. minced horse-meat.
9/5	16.95	940	+	+	+ 1.35	12.03	12.12	8/5 100 g. glucose, 700 g. minced horse-meat.
4/6	16.40	1190	+	+	+ 0			3/6 350 g. bread, 500 ccm. skim-milk.
5/6	16.40	1100	—	—	0			4/6 100 g. glucose, 700 g. minced horse-meat.
14/6	16.25	1040	—	—	0			13/6 100 g. glucose, 700 g. minced horse-meat.
27/6	16.00	1630	—	—	0			26/6 100 g. glucose, 700 g. minced horse-meat.
1/7	15.85	1570	+	+	0	trace		30/6 100 g. glucose, 700 g. minced horse-meat.
3/8	15.85	2230	+	+	+ 5.7	119.97		2/8 400 g. bread, 500 ccm. skim-milk.

Date	Weight kg.	Urine								Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone. Diacetic acid.	
4/8	11.85	2030 D.1800	1023	3.40	69.02	15.34	0.72	4.49	—	3/8 500 g. horse-meat, 30 g. fat (emulsion) 1850 ccm. water.
5/8	11.70	1375 D.1150	1026	3.69	50.73	14.92	1.23	3.40	—	4/8 500 g. horse-meat, 30 g. fat meat, 1200 ccm. water.
6/8	11.70	1680 D.1440	1024	3.40	57.12	18.22	1.17	3.13	—	5/8 500 g. horse-meat, 40 g. fat, 1400 ccm water.

Date	Weight kg.	Urine								Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone. Diacetic acid.	
^{7}/8	11.80	1875 D.1520	1021	2.93	54.93	17.32	1.29	3.17	—	^{6}/8 500 g. horse-meat, 40 g. fat, 1350 ccm. water.
^{8}/8	11.75	1870 D.1565	1021	2.98	55.72	18.70	1.24	2.97	+ +	^{7}/8 500 g. horse-meat, 40 g. fat, 1200 ccm. water.
^{9}/8	11.80	1405 D.1120	1018	2.46	34.56	12.29	1.25	2.85	+ +	^{8}/8 300 g. horse-meat, 70 g. fat, 1050 ccm. water.
^{10}/8	11.80	1470 D.1140	1019	2.36	34.69	12.60	1.03	2.75	+ +	^{9}/8 300 g. horse-meat, 70 g. fat, 1110 ccm. water.
^{11}/8	11.80	1275 D.950	1021	2.36	30.08	11.69	0.99	2.57	+ +	^{10}/8 300 g. horse-meat, 70 g. fat, 1000 ccm. water.
^{12}/8	11.80	1165 D.825	1021	2.93	34.12	10.07	0.92	3.38	+ +	^{11}/8 300 g. horse-meat, 70 g fat, 770 ccm. water.
^{13}/8	11.80	1515 D.1125	1015	2.08	31.51	10.23	0.74	3.08	+ +	^{12}/8 200 g. horse-meat, 22 g. casein, 70 g. fat, 860 ccm. water.
^{14}/8	11.80	1310 D.1120	1019	2.55	33.40	10.31	0.82	3.23	+ +	^{13}/8 200 g. horse-meat, 22 g. casein, 70 g. fat, 1040 ccm. water.
^{15}/8	11.80	1320 D.1110	1018	2.46	32.47	10.30	0.72	3.15	+ +	^{14}/8 200 g. horse-meat, 22 g. casein, 70 g. fat, 990 ccm water.
^{16}/8	11.80	1260 D.960	1020	2.60	32.76	10.98	0.82	2.98	+ +	^{15}/8 100 g. horse-meat, 44 g. casein, 70 g. fat, 1050 ccm. water.
^{17}/8	11.80	1270 D.920	1020	2.55	32.38	10.25	0.91	3.15	+ +	^{16}/8 66 g. casein, 70 g. fat, 1050 ccm. water.
^{18}/8	11.80	1495 D.1240	1018	2.36	35.28	10.19	1.33	3.46	+ +	^{17}/8 300 g. horse-meat, 70 g. fat, 1100 ccm. water.
^{19}/8	11.60	1535 D.1240	1016	2.08	31.92	9.67	1.37	3.30	+ +	^{18}/8 200 g. horse-meat, 22 g. casein, 1220 ccm. water, 70 g. fat.

Date	Weight kg.	Urine								Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone. Diacetic acid.	
$^{20}/_{8}$	11.65	1665 D.1235	1017	3.31	55.11	9.84	1.61		+ +	$^{19}/_{8}$ 200 g. horse-meat, 22 g. casein, 31 g. lactose, 1180 ccm. water, 70 g. fat.
$^{21}/_{8}$	11.70	1685 D.1230	1017	3.40	57.29	9.67	1.66		+ +	$^{20}/_{8}$ 200 g. horse-meat, 22 g. casein, 31 g. lactose, 70 g. fat, 1380 ccm. water.
$^{22}/_{8}$	11.70	1600 D.1250	1021	3.69	59.04	10.19	1.72		+ +	$^{21}/_{8}$ 200 g. horse-meat, 22 g. casein, 31 g. lactose, 70 g. fat, 1270 ccm. water.
$^{23}/_{8}$	11.65	1710 D.1350	1020	3.55	60.70	10.53	1.62		+ +	$^{22}/_{8}$ 300 g. horse-meat, 31 g. lactose, 70 g. fat, 1330 ccm. water.
$^{24}/_{8}$	11.60	1790 D.1320	1021	3.50	62.65	10.90	1.89		+ +	$^{23}/_{8}$ 300 g. horse-meat, 31 g. lactose, 70 g. fat, 1280 ccm. water.
$^{25}/_{8}$	11.60	1740 D.1395	1021	3.50	60.90	10.47	1.95		+ +	$^{24}/_{8}$ 300 g. horse-meat, 31 g. lactose, 70 g. fat, 1420 ccm. water.
$^{26}/_{8}$	11.50	1775 D.1490	1022	3.50	62.12	10.37	1.83		+ +	$^{25}/_{8}$ 200 g. horse-meat, 70 g. fat, 630 ccm. skim-milk, 850 ccm. water.
$^{27}/_{8}$	11.60	1510 D.1735	1024	3.97	59.04	10.46	1.86		+ +	$^{26}/_{8}$ 200 g. horse-meat, 70 g. fat, 630 ccm. skim-milk, 1250 ccm. water.
$^{28}/_{8}$	11.60	1800 D.1400	1021	3.24	58.32	10.01	1.84		+ +	$^{27}/_{8}$ 200 g. horse-meat, 70 g. fat, 630 ccm. skim-milk, 930 ccm. water.
$^{29}/_{8}$	11.55	1550 D.1250	1018	2.22	34.41	10.63	1.89	3.23	+ +	$^{28}/_{8}$ 300 g. horse-meat, 70 g. fat, 1170 ccm. water.
$^{30}/_{8}$	11.50	1585 D.1130	1018	1.99	31.54	10.39	2.19	3.03	+ +	$^{29}/_{8}$ 300 g. horse-meat, 70 g. fat, 1100 ccm. water.
$^{31}/_{8}$	11.55	1180 D.1010	1022	2.79	32.92	9.49	1.97	3.46	+ +	$^{30}/_{8}$ 300 g. horse-meat, 70 g, fat, 1015 ccm. water.

Date	Weight kg.	Urine								Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH₃ g.	D/N	Acetone. Diacetic acid.	
1/9	11.75	1175 D.900	1022	2.98	35.01	10.19	1.92	3.43	+ +	31/8 200 g. horse-meat, 22 g. ovalbumen, 70 g. fat, 855 ccm. water.
2/9	11.50	1410 D.1185	1022	2.69	37.92	11.26	2.04	3.36	+ +	1/9 200 g. horse-meat, 22 g. ovalbumen, 70 g. fat, 1200 ccm. water.
3/9	11.40	1225 D.955	1017	1.98	24.26	7.25	1.81	3.34	+ +	2/9 200 g. horse-meat, 22 g. ovalbumen, 70 g. fat, 1040 ccm. water.
4/9	11.25	1)1040 825		1.94 0.52	24.46	9.18		2.66	+ +	3/9 300 g. horse meat, 70 g. fat. 1) Urine in the drink-water.
5/9	11.20	1970 D.1550	1015	1.75	34.47		2.20		+	4/9 300 g. horse-meat, 70 g. fat, 1550 ccm. water.
6/9	11.10	1775 D.1470	1015	1.99	35.32	9.75	2.02	3.62	+ +	5/9 200 g. horse-meat, 22 g. gelatine, 70 g. fat, 1420 ccm. water.
7/9	11.00	1925 D.1630	1015	1.84	35.42	9.30	2.36	3.80	+ +	6/9 200 g. horse-meat, 22 g. gelatine, 70 g. fat, 1700 ccm. water.
8/9	10.80	1970 D.1700	1016	1.84	36.24	11.30	2.41	3.20	+ +	7/9 200 g. horse-meat, 22 g. gelatine, 70 g. fat, 1660 ccm water.
9/9	10.85	1630 D.1050	1017	2.08	33.90	9.81	2.33	3.46	+ +	8/9 300 g. horse-meat, 70 g. fat, 1000 ccm. water.
10/9	10.90	3120 D.1980		2.65	82.68	13.32	2.49		+ +	9/9 300 g. horse-meat, 70 g. fat, 50 g. glucose, 1900 ccm. water.
11/9	10.45	3575 D.2975	1020	3.79	135.49	13.01	3.14		+ +	10/9 300 g horse-meat, 70 g. fat, 100 g. glucose, 2800 ccm. water.
12/9	10.50	3050 D.2450	1011	1.37	41.78	13.23	2.61	3.15	+ +	11/9 300 g. horse-meat, 70 g. fat, 2400 ccm. water.
13/9	10.65	3170 D.2680	1020	2.79	88.44	27.95	3.12	3.16	+ +	12/9 1200 g. horse-meat, 2500 ccm. water.

Date	Weight kg.	Urine								Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N. g.	NH_3 g.	D/N	Acetone. Diacetic acid.	
14/9	10.60	3025 D.2650	1022	2.22	67.15	14.82	2.72	4.53	+ +	13/9 1200 g. horse-meat, 1710 ccm. water. Withdrawn from the cage.
18/9	9.60	1280 D.1000	1010	1.18	15.10	4.03	1.40	3.74	+ +	17/9 No food, 1000 ccm. water.
19/9	9.50	1590 D.960	1005	0.28	4.45	4.11	1.13	1.82	+ +	18/9 No food. 1100 ccm. water.
20/9	9.70	1210 D.980	1006	0.14	1.69	3.34	0.97		+ +	19/9 150 g. fat, 1160 ccm. water.
21/9	9.40	1050 D.790	1005	0	sugar-free	2.42	0.79		+ +	20/9 200 g. fat, 630 ccm. water.
22/9	9.20	635 D.475	1007	0	trace	2.20	0.58		+ +	21/9 No food, 560 ccm. water.
23/9	9.35	900 D.650	1007	0.18	1.71	3.59	0.76		+ +	22/9 100 g. horse-meat, 120 g. fat, 760 ccm. water.
24/9	9.55	800 D.610	1008	0	trace	3.58	0.75		+ +	23/9 100 g. horse-meat, 120 g. fat, 980 ccm. water.
25/9	9.65	995 D.580	1007	0	trace	2.75	0.58		+ +	24/9 100 g. horse-meat, 120 g. fat, 560 ccm. water.
26/9	9.75	1000 D.850	1011	0.56	5.60	4.83	0.62	1.16	+ +	25/9 200 g. horse-meat, 120 g. fat, 700 ccm. water. Withdrawn from the cage.
3/10	9.65	1210	1005	0.19	2.30				+ +	2/10 120 g. fat, water.
4/10	9.60	970	1006	0	trace	2.10	0.77		+ +	3/10 120 g. fat, 810 ccm. water.
5/10	9.50	1650 D.1270		0.47	7.75	5.43	1.65	1.42	Total-aceton 1.94 g. + +	4/10 200 g. horse-meat, 120 g. fat, 1230 ccm. water.
6/10	9.60	1650 D.1450	1013	0.75	12.37	6.17	2.01	2.00	2.38 + +	5/10 200 g. horse-meat, 120 g. fat, 1780 ccm water.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Total Acetone g.	Alb.	
7/10	9.35	1760 D.1500	1012	0.75	13.20	6.95	1.76	1.89	2.01 + +	+	6/10 200 g. horsemeat, 120 g. fat, 1600 ccm. water.
8/10	9.00	2100 D.2010	1011	1.08	22.68	8.96	1.97	2.52	1.42 + +	+	7/10 200 g. horsemeat, 120 g. fat, 2150 ccm. water.
9/10	8.85	1960 D.1680	1010	1.04	20.38	7.81	1.25	2.60	0.91 + +	+	8/10 200 g. horsemeat, 120 g. fat, 0.1 g. Hypophysis sicc., 1900 ccm. water.
10/10	8.80	1220 D.1110	1015	1.46	17.81	6.81	1.10	2.61	0.79 + +	+	9/10 200 g. horsemeat, 120 g. fat, 0.1 g. Hypophysis sicc., 1150 ccm. water.
11/10	8.80	1180 D.900	1015	1.75	20.65	7.43	1.17	2.76	0.60 +	+ slight	10/10 200 g. horsemeat, 120 g. fat, 0.1 g. Hypophysis sicc., 1050 ccm. water.
12/10	8.80	1200 D.900	1012	1.23	14.76	6.34	1.02	2.32	0.69 +	+ slight	11/10 200 g. horsemeat, 120 g. fat, 0.2 g. Hypophysis sicc., 980 ccm. water.
13/10	8.80	1260 D.910	1011	0.90	11.34	6.35	1.06	1.78	0.59 +	+ slight	12/10 200 g. horsemeat, 120 g. fat, 0.2 g. Hypophysis sicc., 1000 ccm. water.
14/10	8.90	1230 D.650	1009	0.61	7.50	5.38	0.96	1.37	0.41 +	+ trace	13/10 200 g. horsemeat, 120 g. fat, 0.2 g. Hypophysis sicc., 760 ccm. water.
15/10	8.90	1020 D.730	1010	0.65	6.63	4.89	0.73	1.15	0.34 +	+ trace	14/10 200 g. horsemeat, 120 g. fat, 0.3 g. Hypophysis sicc. 810 ccm. water.
16/10	9.00	1170 D.860	1011	0.85	9.94	5.40	0.90	1.84	0.60	+ slight	15/10 200 g. horsemeat, 120 g. fat, 0.3 g. Hypophysis sicc., 930 ccm. water.

Date	Weight kg.	Urine									Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Total Acetone g.	Alb.	
17/10	9.05	1320 D.830	1009	0.70	9.24	5.49	1.04	1.65	0.66	+	16/10 200 g. horse-meat, 120 g. fat, 0.3 g. Hypophysis sicc., 930 ccm. water.
18/10	9.15	1460 D.950	1010	0.94	13.72	6.23	1.06	2.20	0.95	+	17/10 200 g. horse-meat, 120 g. fat, 0.4 g. Hypophysis sicc., 950 ccm. water.
19/10	9.10	1070 D.750	1014	1.08	11.55	5.99	1.37	1.92	0.88	+	18/10 200 g. horse-meat, 120 g. fat, 0.4 g. Hypophysis sicc., 730 ccm. water.
20/10	9.05	1345 D.980	1015	1.23	16.54	7.81	1.84	2.14	1.18	+	19/10 200 g. horse-meat, 120 g. fat, 0.7 g. Hypophysis sicc., 870 ccm. water.
21/10	8.95	1085 D.880	1015	1.37	14.86	6.30	1.53	2.35	1.02	+	20/10 200 g. horse-meat, 120 g. fat, 1.0 g. Hypophysis sicc., 950 ccm. water.
22/10	8.95	1560 D.1340	1013	1.37	21.37	7.26	2.00	2.94	1.42	+	21/10 200 g. horse-meat, 120 g. fat, 1.0 g. Hypophysis sicc., 1260 ccm. water.
23/10	8.80	1530 D.1150	1011	1.13	17.28	5.83	1.64	2.96	1.19	+	22/10 200 g. horse-meat, 120 g. fat, 1200 ccm. water.
24/10	8.90	1300 D.1030	1014	1.32	17.16	6.46	1.59	2.64	1.24	+	23/10 200 g. horse-meat, 120 g. fat, 1280 ccm. water.
25/10	8.75	1260 D.1100	1012	1.04	13.10	5.64	1.58	2.32	1.09	+	24/10 200 g. horse-meat, 120 g. fat, 1000 ccm. water.
28/10	8.85	1200 D.1200	1012	0.85	10.20				1.28	+	27/10 200 g. horse-meat, 120 g. fat, 1300 ccm. water. Withdrawn from the cage. — Gets 500 g. minced horse-meat daily.

Date	Weight kg.	Urine.									Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Total Acetone g.	Alb.	
$^{16}/_{1}$-18	7.80	1030	1014	1.13	11.64	5.91	1.71	1.97	+ +	+	$^{15}/_{1}$ 200 g. horse-meat, 120 g. fat, 1030 ccm. water.
$^{17}/_{1}$	7.70	1250	1014	0.94	11.75	4.55	2,00	2.58	+ +	+	$^{16}/_{1}$ 200 g. horse-meat, 120 g. fat, 1270 ccm. water.
$^{18}/_{1}$	7.60	720	1017	1.27	9.14	3.88		2.36	+ +	+	$^{17}/_{1}$ 200 g. horse-meat, 120 g. fat, 540 ccm. water.
$^{19}/_{1}$	7.60	1140	1027	2.84	32.37	10.05		3.12	+ +	+	$^{18}/_{1}$ 500 g. horse-meat, 120 g. fat, 1260 ccm. water.
$^{20}/_{1}$	7.60	910	1030	3.69	33.57	11.65		2.88	+ +	+	$^{19}/_{1}$ 500 g. horse-meat, 120 g. fat, 740 ccm. water.
$^{21}/_{1}$	7.55	950	1027	3.40	32.30	10.00		3.23	+ +	+	$^{20}/_{1}$ 500 g. horse-meat, 120 g. fat, 740 ccm. water. Withdrawn from the cage.

For the first 14 days the dog gets 700 g. minced horse-meat. Thereafter it gets in addition 50 g. emulsified fat (emulsified with 10 ccm. 10 % Na_2Co_3-solution). Thereby it gains steadily in weight, becomes more lively and buoyant, whereas at the end of the preceding period it was almost cachectic. In the course of 1 month it gains 1 kg. in weight.

Date	Weight kg.	Urine							Remarks.
		Quant. ccm.	Sp. G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	
2/3	8.20	1730	1021	2.08	35.98	14.53	3.43	2.47	1/3 500 g. horse-meat, 50 g. fat, 1600 ccm. water.
3/3	8.15	1760	1021	2.27	39.95	14.90	3.26	2.68	2/3 500 g horse-meat, 50 g. fat, 1670 ccm. water.
4/3	8.00	1350	1022	2.17	29.29	13.79	2.63	2.12	3/3 500 g. horse-meat, 50 g. fat, 1170 ccm. water.
5/3	8.15	1210	1025	2.74	33.15	14.18	1.36	2.05	4/3 500 g. horse-meat, 50 g. fat, 5 g. 1260 ccm. water.
6/3	8.20	1590	1021	1.98	35.45	14.80	2.21	2.66	5/3 500 g. horse-meat, 50 g. fat, 5 g. 1420 ccm. water.
7/3	8.50	1300	1025	2.65	34.45				6/3 500 g. horse-meat, 50 g. fat, 5 g. 1250 ccm. water.
8/3	8.35	1430	1025	3.50	50.05				7/3 500 g. horse-meat, 50 g. fat, 1340 ccm. water.
9/3	8.50	1070	1031	4.68	50.07				8/3 500 g. horse-meat, 50 g. fat, 1070 ccm. water.
10/3	8.50	1340	1027	3.17	42.47				9/3 500 g. horse-meat, 50 g. fat, 1020 ccm. water.

13/3. Diarrhoea. Does not eat.

14/3. Does not eat.

15/3. Moping, feeble. Drinks only a little water. No defecation.

16/3. Lies without moving. Fully conscious. Will eat nothing. No defecation. Has eaten nothing since 12/3. Extremely feeble. Died in the course of the evening.

Dog II.

Deerhound, female, age 4 months. Weight 4.75 kg.

Partial pancreatectomy 8/11 1916. Removal of the vertical part and the greater part of the horizontal part of pancreas. Remnant 3 cm. (processus lienalis). Part removed had a length of 20 cm. and weighed 14.5 g. Vessels intact.

Date	Weight kg.	Urine						Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	Glucose g. BANG	
9/11	4.55		—	—	0			8/11 Operation, 250 ccm. water.
10/11	4.40	595	—	—	—0.1			9/11 250 ccm. skim-milk.
11/11	4.35		+	+		+		10/11 500 ccm. skim-milk.
12/11	4.47	400	—	—	0			11/11 400 g. horse-meat.
17/11	4.15	405	+	+	+ 0.3	1.13	1.26	16/11 100 g. bread, 600 ccm. skim-milk.
22/11	4.10	830	+	+	+ 0.1	1.56	2.28	21/11 28 g. glucose with stomach-tube, 280 g. minced horse-meat.
23/11	4.25	790	+	+	+ 0.1	1.50	1.97	22/11 28 g. glucose, 280 g. minced horse-meat.
In the beginning of December the dog got severe gastro-enteritis, which lasted 2 or 3 weeks.								
17/1	6.00	750	+	+	+ 0.1	1.42	1.72	16/1 60 g. glucose, 350 g. minced horse-meat.
19/1	6.10	870	+	+	+ 0.9	7.42	7.70	18/1 80 g. glucose, 350 g. minced horse-meat.
13/3	8.30	1380	+	+	0			12/3 350 g. bread, 750 ccm. skim-milk.
27/3	8.50	1750	—	—	0		0.96	26/3 80 g. glucose, 500 g. minced horse-meat.
28/3	8.45	1640	+	+	+ 0.6	6.36	6.56	27/3 100 g. glucose, 500 g. minced horse-meat.
29/3	8.50	1970	+	+	+ 0.5	9.32	9.48	28/3 115 g. glucose, 500 g. minced horse-meat.

Date	Weight	Urine						Remarks
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	Glucose g. BANG	
13/4	8.80	1280	—	—	0			12/4 350 g. bread, 750 ccm. skim-milk.
5/5	9.35	300	+	+	+ 0.8	2.28	3.09	4/5 350 g. bread, 750 ccm. skim-milk.
6/5	9.20	290	+	+	0		0.72	5/5 400 g. bread, 750 ccm. skim-milk.
7/5	9.40	400	—	—	— 0.1			6/5 500 g. bread, water.
8/5	9.35	470	—	—	— 0.1			7/5 500 g. bread.
9/5	9.40	1415	+	+	+ 0.1	1.27	1.91	8/5 80 g. glucose, 500 g. minced horse-meat.
10/5	9.30	1550	+	+	+ 0.2	2.95	3.25	9/5 100 g. glucose, 500 g. minced horse-meat.
4/6	9.80	1480	—	—	0			3/6 350 g. bread, 750 ccm. skim-milk.
5/6	9.70	1910	—	—	0			4/6 80 g. glucose, 500 g. minced horse-meat.
20/7	9.80	1845	—	—	0			19/7 80 g. glucose, 500 g. minced horse-meat.
2/8	9.65	1960	—	—	0			1/8 90 g. glucose, 500 g. minced horse-meat.
4/8	9.80	1160	—	—	0			3/8 350 g. bread — 500 cm^3 skim-milk.
24/8	9.65	1665 D.1400	+	+	+ 0.1	1.50		23/8 100 g. glucose, 500 g. minced horse-meat.
27/8	9.60	950 D.670	+	+	+ 0	trace		26/8 100 g. glucose, 600 g. minced horse-meat.
8/11	9.80	1450 D.1450	+	+	0	trace		7/11 100 g. glucose, 600 g. minced horse-meat.
22/11	9.60		+	+			2.17	22/11 150 g. glucose, 600 g. minced horse-meat.

Withdrawn from the cage. The dog, which hitherto in the intervals between the tolerance-tests has lived exclusively on bread and milk, hereafter gets 700 g. minced horse-meat per day.

Date	Weight kg.	Urine						Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	Glucose g. BANG.	
$^{14}/_{4}$	12.30	1250	+	+	+ 0.6	7.00		$^{13}/_{4}$ 100 g. glucose, 700 g. minced horse-meat.
$^{7}/_{5}$	12.00	1170	+	+	+ 0.5	5.52		$^{6}/_{5}$ 75 g. glucose, 700 g. minced horse-meat.
$^{11}/_{5}$	12.20		+	+		7.83		$^{10}/_{5}$ 50 g. glucose, 700 g. minced horse-meat.

Date	Weight kg.	Urine				Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	Glucose g. polarim.	
$^{12}/_{5}$	12.30		+	+	1.36	$^{11}/_{5}$ 25 g. glucose, 700 g. minced horse-meat.
$^{13}/_{5}$	12.35		+	+	0.47	$^{12}/_{5}$ 20 g. glucose, 700 g. minced horse meat.
$^{14}/_{5}$	12.40	—	—			$^{13}/_{5}$ 15 g. glucose, 700 g. minced horse-meat.
$^{16}/_{5}$	12.70		+	+	0.48	$^{15}/_{5}$ 20 g. glucose, 700 g. minced horse-meat.
$^{24}/_{5}$	12.50		+	+	0.29	$^{22}/_{5}$ 15 g. glucose, 700 g. minced horse-meat.
$^{25}/_{5}$	12.60		—	—		$^{24}/_{5}$ 10 g. glucose, 700 g. minced horse-meat.
$^{26}/_{5}$	12.70		+	+	16.82	$^{25}/_{5}$ 100 g. glucose, 700 g. minced horse-meat.
$^{29}/_{5}$	12.70	880	—	—		$^{28}/_{5}$ 100 g. starch (200 g. bread), 200 g. minced horse-meat.
$^{31}/_{5}$	12.60	620	—	—		$^{30}/_{5}$ 200 g. starch (400 g. bread).
$^{4}/_{6}$	12.70		+	+	0.23	$^{3}/_{6}$ 10 g. glucose, 700 g. minced horse meat.
$^{6}/_{6}$	12.70	790	+	+	trace	$^{5}/_{6}$ 200 g. starch (400 g. bread).

Date	Weight kg.	Urine					Remarks
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	
$^{8}/_{6}$	12.75	960	—	—			$^{7}/_{6}$ 1000 g. horse-meat.
$^{11}/_{6}$	13.00		—	—			$^{10}/_{6}$ 5 g. glucose, 700 g. minced horse meat.
$^{12}/_{6}$	13.00		+	+	0.2	1.22	$^{11}/_{6}$ 200 g. starch, (400 g. bread).
$^{14}/_{6}$	Relaparatomy. Killed. Dissection.						

Dog III.

Foxterrier, female, age 5$^{1}/_{2}$ months. Weight 4.90 kg.

Partial pancreatectomy $^{3}/_{7}$ 1917. Removal of the horizontal part and the greater part of the vertical part of pancreas. Remnant 1$^{1}/_{2}$ cm. (caput.). Parts removed had a length of 9.5 cm. together and weighed 7.2 g.

Date	Weight kg.	Urine					Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	
$^{3}/_{7}$	4.90						$^{3}/_{7}$ Operation.
$^{19}/_{7}$	3.90	855 D:420	—	—	0		$^{18}/_{7}$ 350 g. horse-meat, 400 ccm. water.
$^{23}/_{7}$	3.90	1850 D.1420	+	+	+ 0.4	7.03	$^{22}/_{7}$ 1000 ccm. skim-milk.
$^{24}/_{7}$	3.95	950 D.770	+	+	+ 0.5	4.46	$^{23}/_{7}$ 1000 ccm. skim-milk.
$^{25}/_{7}$	4.05	805 D.475	+	+	+ 0.3	2.25	$^{24}/_{7}$ 500 ccm. skim-milk, 70 g. bread, 130 ccm. water.
$^{26}/_{7}$	4.00	1255 D.550	+	+	+ 0.1	1.13	$^{25}/_{7}$ 500 ccm. skim-milk, 70 g. bread, 200 ccm. water.
$^{27}/_{7}$	3.95	670 D.385	+	+	+ 0.2	1.20	$^{26}/_{7}$ 500 ccm. skim-milk, 70 g. bread, 130 ccm. water.
$^{1}/_{8}$	3.80	470 D.375	—	—	0		$^{31}/_{7}$ 250 ccm. skim-milk, 150 g. bread, 250 ccm. water.

Date	Weight kg.	Urine						Remarks
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	N g.	
2/8	3.85	510 D.460	—	—	0			1/8 250 ccm. skim-milk, 150 g. bread, 250 ccm. water.
4/8	3.85	175 D.125	—	—	0			3/8 250 ccm. skim-milk, 250 g. bread, 250 ccm. water.
5/8	3.95	480 D.290	—	—	0			4/8 250 ccm. skim-milk, 250 g. bread, 250 ccm. water.
8/8	3.80	415 D.310	—	—	0		8.50	7/8 10 g. glucose, 300 g. horse-meat, 110 ccm. water.
9/5	3.80	435 D.320	—	—	0		8.48	8/8 20 g. glucose, 300 g. horse-meat, 200 ccm. water.
10/8	3.80	440 D.300	—	—	0		8.83	9/8 30 g. glucose, 300 g. horse-meat, 300 ccm. water.
13/8	3.90	385 D.220	—	—	0		8.41	12/8 40 g. glucose, 300 g. horse-meat, 90 ccm. water.
14/8	3.95	450 D.315	—	—	0		8.75	13/8 50 g. glucose, 300 g. horse-meat, 260 ccm. water.
15/8	3.95	250 D.250	+	+	+ 2.40	5.67	7.94	14/8 50 g. lactose, 300 g. horse-meat, 110 ccm. water.
16/8	4.00	360 D.225	—	—	0		7.30	15/8 60 g. glucose, 300 g. horse-meat, 170 ccm. water.
17/8	4.00	300 D.250	+	+	+ 2.0	5.61	8.50	16/8 60 g. lactose, 300 g. horse-meat, 230 ccm. water.
18/8	4.00	445 D.300	—	—	0		8.95	17/8 60 g. glucose, 300 g. horse-meat, 140 ccm. water.
19/8	4.10	535 D.260	—	—	0		8.20	18/8 70 g. glucose, 300 g. horse-meat, 250 ccm. water.
20/8	4.15	425 D.280	+	+	+ 1.6	6.41	8.41	19/8 70 g. lactose, 300 g. horse-meat, 300 ccm. water.
21/8	4.25	500 D.270	—	—	0		8.89	20/8 80 g. glucose, 300 g. horse-meat, 270 ccm. water.

Date	Weight kg.	Urine						Remarks.
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	N g.	
$^{22}/_8$	4.25	645 D.320	+	+	+ 1.4	8.51	8.00	$^{21}/_8$ 80 g. lactose, 300 g. horse-meat, 490 ccm. water.
$^{23}/_8$	4.30	510 D.275	—	—	0		8.74	$^{22}/_8$ 90 g. glucose, 300 g. horse-meat, 140 ccm. water.
$^{24}/_8$	4.35	570 D.300	—	—	0		8.22	$^{23}/_8$ 100 g. glucose, 300 g. horse-meat, 40 ccm. water.
$^{25}/_8$	4.35	1130 D.1130	+	+	+ 0.8	8.47	7.75	$^{24}/_8$ 1600 cm^3 skim-milk, 37 g. horse-meat (cfr. $^{22}/_8$).
$^{25}/_{10}$	5.80	730 D.340	—	+	0	trace	8.36	$^{24}/_{10}$ 100 g. glucose, 300 g. horse-meat.
$^{28}/_5$ 18	7.70		—	—		2.49		$^{27}/_5$ 100 g. glucose, 300 g. horse-meat.
$^{29}/_5$	7.75	520	+	+	0			$^{28}/_5$ 75 g. glucose, 300 g. horse-meat, 480 ccm. water.
$^{10}/_7$	8.80	785	+	+	0.45	3.37		$^{9}/_7$ 100 g. glucose, 500 g. minced horse meat, 700 ccm. water.
$^{12}/_7$	8.85	690	+	+	0.2	1.24		$^{11}/_7$ 75 g. glucose, 500 g. minced horse-meat, 475 ccm. water.
$^{13}/_7$	8.85	250	+	+	0.2	0.45		$^{12}/_7$ 60 g. glucose, 500 g. minced horse-meat, 300 ccm. water.
$^{15}/_7$	8.90	450	+	+	0	trace		$^{14}/_7$ 50 g. glucose, 500 g. minced horse-meat, 350 ccm. water.
$^{16}/_7$	8.80	465	—	—	0			$^{15}/_7$ 40 g. glucose, 500 g. minced horse-meat, 350 ccm. water. $^{16}/_7$ Killed.

Dog IV.

Deerhound, female, age 9 months. Weight 13.75 kg.

Partial pancreatectomy 18/4 1917. The horizontal part and the extremity of the vertical part removed. Remnant (caput) 1 1/2 cm. Parts removed: length 18 cm., weight 18.5 g. Vessels intact.

Date	Weight kg.	Urine						Remarks
		Quant. ccm.	Reduction-tests	Phenylhydrazin-test	α_D	Glucose g. polarim.	Glucose g. BANG.	
13/4	13.70	1325	—	—	0			12/4 150 g. glucose, 600 g. minced horse-meat.
19/4	12.90	870	—	—	0			18/4 Operation.
20/4	12.75	1165	—	—	— 0.1			19/4 No food.
21/4	12.50	1410	+	+	+ 0.85	11.28	11.84	20/4 500 ccm. skim-milk + water.
22/4	12.50	1230	+	+	+ 3.1	36.04	34.80	21/4 1000 ccm. skim-milk + water.
23/4	12.75	920	+	+	+ 4.0	34,84		22/4 1000 ccm. skim-milk + water.
24/4	12.25	470	—	—	— 0.1			23/4 Diarrhœa. No food.
26/4	12.55	1235	+	+	+ 3.1	36.18	35.20	25/4 100 g. dogbiscuits, (60 g. starch), + water.
27/4	11.90	980	+	+	+ 2.6	24.10	24.50	26/4 60 g. dogbiscuits, (36 g. starch) + water.
28/4	11.60	1060	+	+	+ 0.2	2.01	2.28	27/4 150 g. minced horse-meat + water.
29/4	11.75	960	—	—	— 0.1			28/4 No food.
1/5	11.50	1630	+	+	+ 3.1	47.92	48.90	30/4 50 g. glucose with stomach-tube, 400 g. minced horse-meat.
2/5	11.35	940	+	+	+ 3.6	32.05	32.90	1/5 50 g. glucose, 100 g. minced horse-meat.
3/5	11.20	985	+	+	+ 8.1	75.55	77.03	2/5 200 g. bread, 1000 ccm. skim-milk.
5/5	11.70	640	+	+	+ 7.0	42.43	43.52	4/5 350 g. bread + water.

Date	Weight kg.	Urine								Remarks.
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone Diacetic acid.	
10/5	11.50	1060	1029	3.31	34.08	12.87	0.31	2.65	—	9/5 600 g. horse-meat, 1000 ccm. water.
11/5	11.50	950	Qua. ccm. 5400	1.79	96.60	47.06	1.80	2.05	—	10/5 600 g. horse-meat, 800 ccm. water.
12/5	11.75	850								11/5 600 g. horse-meat, 700 ccm. water.
13/5	11.70	740								12/5 600 g. horse-meat, 630 ccm. water.
14/5	11.70	750	6020	0.80	48.16	30.17	1.24	1.59	—	13/5 300 g. horse-meat, 33 g. fat, (in emulsion).
15/5	11.65	1230								14/5 300 g. horse meat, 33 g. fat.
16/5	11.82	1170								15/5 300 g. horse-meat, 33 g. fat.
17/5	11.80	790	4940	3.54	174.87	29.43	1.00		—	16/5 300 g. horse-meat, 75 g. boiled starch.
18/5	11.70	810								17/5 300 g. horse-meat, 75 g. boiled starch.
19/5	11.65	760								18/5 300 g. horse-meat, 75 g. boiled starch.
			Sp G.							
20/5	11.65	K.790 D.700	1043	5.87	46.37	14.87	0.35	3.12	—	19/5 600 g. horse-meat.
21/5	11.65	1000 D.780	1040	5.58	55.80	18.20	0.42	3.06	—	20/5 600 g. horse-meat.
22/5	11.65	840 D.730	1039	5.30	44.52	16.97	0.43	2.62	—	21/5 600 g. horse-meat.
23/5	11.60	1020 D.850	1029	3.88	39.58	16.03	0.53	2.46	—	22/5 500 g. horse-meat.
24/5	11.45	1060 D.820	1031	4.45	47.17	14.02	0.30	3.36	—	23/5 500 g. horse-meat.
25/5	11.45	1055 D.855	1030	4.07	42.94	14.62	0.33	2.94	—	24/5 400 g. horse-meat.
26/5	11.30	1345 D.1050	1021	3.03	40.75	13.84	0.25	2.94	—	25/5 400 g. horse-meat.

Date	Weight kg.	Urine								Remarks.
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone Diacetic acid.	
27/5	11.30	1625 D.1300	1019	2.32	37.70	16.38	0.54	2.36	—	26/5 400 g. horse-meat, 60 g. fat, (in emulsion).
28/5	11.30	1420 D.1250	1022	2.84	40.33	12.32	0.42	3.27	—	27/5 400 g. horse-meat, 60 g. fat.
29/5	11.30	1205 D.850	1012	1.66	20.00	8.43	0.40	2.37	—	28/5 200 g. horse-meat, 60 g. fat.
30/5	11.35	865 D.610	1007	0.28	2.42	5.45	0.18	0.44	—	29/5 100 g. horse-meat, 70 g. fat.
31/5	11.30	880 D.550	1008	0.47	4.13	5.09	0.12	0.81	—	30/5 100 g. horse-meat, 70 g. fat.
1/6	11.35	585 D.355	1010	0.85	4.97	3.79	0.12	1.31	—	31/5 100 g. horse-meat, 70 g. fat, 350 ccm. water.
2/6	11.30	600 D.400	1010	0.28	1.68	3.78	0.15	0.44	—	1/6 100 g. horse-meat, 70 g. fat, 270 ccm. water.
3/6	11.35	1200 D.630	1005	0	0	3.68	0.11		—	2/6 100 g. horse-meat, 100 g. fat, 650 ccm. water.
4/6	11.30	730 D.340	1007	0	0	3.67	0.11		—	3/6 100 g. horse-meat, 130 g. fat, 310 ccm. water.
5/6	11.30	845 D.650	1005	0	0	1.82	0.09		—	4/6 130 g. fat, 690 ccm. water.
6/6	11.30	1110 D.840	1006	0	0	3.77	0.17		—	5/6 100 g. horse-meat, 70 g. fat, 1050 ccm. water.
7/6	11.30	1395 D.1160	1005	0	0	3.83	0.17		—	6/6 100 g. horse-meat, 70 g. fat, 1200 ccm. water.
8/6	11.30	945 D.750	1007	0	0	3.60	0.17		—	7/6 100 g. horse-meat, 70 g. fat, 550 ccm. water.
9/6	11.30	1395 D.930	1007	0.57	7.95	4.00	0.20		—	8/6 100 g. horse meat, 70 g. fat, 20 g. glucose, 1170 ccm. water.
10/6	11.35	1350 D.1260	1007	0.57	7.69	4.02	0.22		—	9/6 100 g. horse-meat, 70 g. fat, 20 g. glucose, 1060 ccm. water.
11/6	11.40	790 D.640	1011	1.09	8.61	4.36	0.15		—	10/6 100 g. horse-meat, 70 g. fat, 20 g. glucose, 495 ccm. water.

Date	Weight kg.	Urine								Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone Diacetic acid.	
12/6	11.35	1310 D.1100	1008	0.94	12.31	4.35	0.23		—	11/6 100 g. horse-meat, 70 g. fat, 20 g. glucose, 810 ccm. water.
13/6	11·35	1100 D.1035	1010	1.27	13.97	4.62	0.24		—	12/6 100 g. horse-meat, 70 g. fat, 20 g. glucose, 1050 ccm. water.
14/6	11.35	1110 D.1005	1006	0	0	4.35	0.22		—	13/6 100 g. horse-meat, 70 g. fat, 1040 ccm. water.
15/6	The dog has remained in the metabolic cage since the operation. In order to give it a little rest it is to-day taken out of the cage and put into the kennel. It gets daily 100 g. horse-flesh and 70 g. emulsified fat.									
30/6	11.30	1050 D.985	1006	0	0	3.45	0.11		—	29/6 100 g. horse-meat, 70 g. fat, 1010 ccm. water.
1/7	11.35	1200 D.940	1004	0	0	3.44	0.15		—	30/6 100 g. horse-meat, 70 g. fat, 1140 ccm. water.
2/7	11.30	1465 D.1040	1005	0	0	3.28	0.12		—	1/7 100 g. horse-meat, 70 g. fat, 20 g. boiled starch, 1020 ccm. water.
3/7	11.28	1500 D.1050	1003	0	0	2.67	0.06		—	2/7 100 g. horse-meat, 70 g. fat, 20 g. boiled starch, 670 ccm. water.
4/7	11.32	1135 D.1000	1005	0	0	3.17	0.05		—	3/7 100 g. horse-meat, 70 g. fat, 810 ccm. water.
5/7	11.30	1215 D.950	1006	0	0	3.23	0.11		—	4/7 100 g. horse-meat, 70 g. fat, 650 ccm. water.
6/7	11.30	1195 D.870	1006	0	0	2.96	0.09		—	5/7 100 g. horse-meat, 70 g. fat, 750 ccm. water.
7/7	11.30	1165 D.850	1004	0	0	2.97	0.08		—	6/7 100 g. horse-meat, 70 g. fat, 780 ccm. water.
8/7	11.30	1180 D.900	1004	0	0	3.09	0.13		—	7/7 100 g. horse-meat, 70 g. fat, 800 ccm. water.

Date	Weight kg.	Urine								Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone Diacetic acid.	
9/7	11.30	1565 D.880	1005	0.19	2.97	3.78	0.11		—	8/7 100 g. horsemeat, 70 g. fat, 20 g. glucose, 550 ccm. water.
10/7	11.30	1315 D.1050	1095	0.24	3.15	3.78	0.16		—	9/7 100 g. horsemeat, 70 g. fat, 20 g. glucose, 850 ccm. water.
11/7	11.30	1120 D.720	1006	0	0	3.01	0.11		—	10/7 100 g. horsemeat, 70 g. fat, 880 ccm. water.
12/7	11.30	1080 D.900	1007	0	0	3.48	0.13		—	11/7 100 g. horsemeat, 70 g. fat, 720 ccm. water,

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone	Alb.	
13/7	11.30	1850 D.840	1004	0	0	4.53	0.26		—	—	12/7 200 g. horsemeat, 60 g. fat, 830 ccm. water.
14/7	11.35	1220 D.730	1005	0	0	5.46	0.26		—	—	13/7 200 g. horsemeat, 60 g. fat, 750 ccm. water.
15/7	11.40	980 D.710	1009	0	0	6.38	0.26		—	—	14/7 300 g. horsemeat, 50 g. fat, 770 ccm. water.
16/7	11.42	925 D.770	1012	0.48	4.44	7.15	0.34	0.68	—	—	15/7 300 g. horsemeat, 50 g. fat, 680 ccm. water.
17/7	11.50	970 D.700	1013	0.48	4.66	7.26	0.41	0.64	—	—	16/7 300 g. horsemeat, 50 g. fat, 680 ccm. water.
18/7	11.60	975 D.620	1014	0.25	2.34	8.53	0.39	0.46	—	—	17/7 400 g. horsemeat, 40 g. fat, 500 ccm. water.
19/7	11.65	1055 D.710	1015	1.04	10.97	10.45	0.55	1.00	—	—	18/7 400 g. horsemeat, 40 g. fat, 700 ccm. water.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH$_3$ g.	D/N	Acetone	Alb.	
20/7	11.65	1245 D.865	1013	0.57	7.09	10.06	0.42	0.70	—	—	19/7 400 g. horse-meat, 40 g. fat, 800 ccm. water.
21/7	11.70	940 D.740	1018	1.23	11.56	9.84	0.42	1.17	—	—	20/7 400 g. horse-meat, 40 g. fat, 500 ccm. water.
22/7	11.70	1125 D.610	1015	1.04	11.70	10.08	0.41	1.16	—	—	21/7 400 g. horse-meat, 40 g. fat, 570 ccm. water.
23/7	11.65	1155 D.865	1020	1.6	18.48	11.16	0.51	1.65	—	—	22/7 400 g. horse-meat, 40 g. fat, 550 ccm. water.
24/7	11.75	935 D.625	1024	2.74	25.62	10.57	0.40	2.42	+	—	23/7 400 g. horse-meat, 40 g. fat, 550 ccm. water.
25/7	11.70	1115 D.890	1025	2.66	29.66	10.38	0.55	2.85	+	—	24/7 400 g. horse-meat, 40 g. fat, 600 ccm. water.
26/7	11.75	1200 D.950	1025	2.18	26.16	12.26	0.76	2.13	+	—	25/7 400 g. horse-meat, 40 g. fat, 700 ccm. water.
27/7	11.60	1075 D.940	1025	2.66	28.59	11.74	1.08	2.43	+	—	26/7 400 g. horse-meat, 40 g. fat, 800 ccm. water.
28/7	11.70	1000 D.650	1025	3.32	33.20	11.16	0.40	2.97	+	—	27/7 400 g. horse-meat, 40 g. fat, 450 ccm. water.
29/7	11.70	1215 D.1010	1024	2.27	27.58	14.21	0.34	1.93	—	—	28/7 400 g. horse-meat. 40 g. fat, 750 ccm. water.
30/7	11.70	1210 D.910	1028	2.93	35.45	11.38	0.31	3.11	—	—	29/7 400 g. horse-meat, 40 g. fat, 670 ccm. water.
31/7	11.70	1290 D.1050	1024	2.55	32.89	13.76	0.59	2.39	—	—	30/7 400 g. horse-meat, 40 g. fat, 690 ccm. water,
1/8	11.65	900 D.750	1030	3.03	27.27	11.34	0.47	2.40	—	—	31/7 400 g. horse-meat, 40 g. fat, 650 ccm. water.
2/8	11.60	D.885			32.25	12.53		2.57	—	—	1/8 400 g. horse-meat, 40 g. fat, 700 ccm. water.
3/8	11.60	1355 D.1000		2.74	37.12	14.29	0.83	2.59	+	—	2/8 400 g. horse-meat, 40 g. fat, 700 ccm. water.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone	Alb.	
4/8	11.55	850 D.680	1029	3.88	32.98	11.10	0.48	2.97	+	—	3/8 400 g. horse-meat, 40 g. fat, 450 ccm. water.
5/8	11.55	875 D.710	1031	4.16	36.40	12.92	0.59	2.81	+	—	4/8 400 g. horse-meat, 40 g. fat, 500 ccm. water.
6/8	11.55	1000 D.650	1027	3.40	34.00	12.88	0.82	2.64	+	—	5/8 400 g. horse-meat, 40 g. fat, 400 ccm. water.
7/8	11.50	Urine goes to loss.									6/8 600 g. horse-meat, 900 ccm. water.
8/8	11.50	1000 D.940	1039	5.68	56.80	18.58	0.85	3.05	+	—	7/8 600 g. horse-meat, 600 ccm. water.
9/8	11.50	1140 D.1040	1035	5.02	57.22	19.95	0.96	2.86	+	—	8/8 600 g. horse-meat, 600 ccm. water.
10/8	11.50	1165 D.1010	1034	4.78	55.68	18.70	0.93	2.97	+	—	9/8 600 g. horse-meat, 670 ccm. water.
11/8	11.40	1250 D.1175	1032	4.54	56.75	20.12	1.07	2.82	+	—	10/8 600 g. horse-meat, 600 ccm. water.
12/8	11.40	1175 D.1000	1035	5.20	61.10	18.99	0.90	3.21	+	—	11/8 600 g. horse-meat, 550 ccm. water.
13/8	11.35	1130 D.1000	1037	5.68	64.18	19.77	0.86	3.24	+	—	12/8 600 g. horse-meat, 600 ccm. water.
14/8	11.25	1500 D.1430	1034	4.92	73.80	25.41	1.35	2.90	+	—	13/8 700 g. horse-meat, 790 ccm. water.
15/8	11.25	1400 D.1295	1036	5.39	75.66	22.54	1.44	3.35	+	—	14/8 700 g. horse-meat, 880 ccm. water.
16/8	11.25	1550 D.1460	1033	5.11	79.20	21.70	1.35	3.64	+	—	15/8 700 g. horse-meat, 970 ccm. water.
17/8	11.25	1390 D.1250		4.82	66.99	23.10	1.39	2.90	—	—	16/8 700 g. horse-meat, 700 ccm. water.
18/8	11.15	1400 D.1335	1037	5.30	74.30	23.26	1.42	3.12	—	—	17/8 700 g. horse-meat, 730 ccm. water.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone	Alb.	
19/8	11.10	1380 D.1235	1032	4.40	60.72	23.57	1.47	2.58	—	—	18/8 700 g. horse-meat, 820 ccm. water.
20/8	11.10	1975 D.1720	1031	4.45	87.88	30.34	1.90	2.89	—	—	19/8 1000 g. horse-meat, 1100 ccm. water.
21/8	11.10	2010 D.1785	1033	4.97	99.89	32.71	1.76	3.05	—	—	20/8 1000 g. horse-meat, 1260 ccm. water.
22/8	11.10	1925 D.1675	1034	4.97	95.69	30.92	1.74	3.09	—	—	21/8 1000 g. horse-meat, 1050 ccm. water.
23/8	11.10	2060 D.1760	1031	4.73	97.43	33.92	1.84	2.87	—	—	22/8 1000 g. horse-meat, 1190 ccm. water.
24/8	10.95	2150 D.1950	1031	4.54	97.61	43.38	2.14	2.83	—	—	23/8 1000 g. horse-meat, 1330 ccm. water.
25/8	11.00	1825 D.1735	1034	5.11	93.25	31.03	1.78	3.00	—	—	24/8 1000 g. horse-meat, 1120 ccm. water.
26/8	11.00	2260 D.2100	1030	4.45	100.57	34.48	1.57	2.91	—	—	25/8 1000 g. horse-meat, 1470 ccm. water.
27/8	10.95	2360 D.2130	1030	4.49	105.96	32.97	1.83	3.21	—	—	26/8 1000 g. horse-meat, 1570 ccm. water.
28/8	10.80	2290 D.2040	1030	4.59	105.11	31.82	2.12	3.30	—	—	27/8 1000 g. horse-meat, 1390 ccm. water.
29/8	10.75	2235 D.2025	1031	4.78	106.83	31.36	1.83	3.40	—	—	28/8 1000 g. horse-meat, 1330 ccm. water.
30/8	10.70	2040 D.1900	1033	5.06	103.22	33.87	2.00	3.04	—	—	29/8 1000 g. horse-meat, 1290 ccm. water.
31/8	10.80	2135 D.1850	1030	4.92	105.04	31.71	1.94	3.31	—	—	30/8 1000 g. horse-meat, 1230 ccm. water.
1/9	10.75	2000 D.1810	1033	5.68	113.60	33.34	2.02	3.40	—	—	31/8 1000 g. horse-meat, 1110 ccm. water.
2/9	10.45	2075	1032			28.93	1.52		—		1/9 1000 g. horse-meat, 1230 ccm. water. Diarrhœa.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone	Alb.	
$^{3}/_{9}$	10.20	1915 D.1720	1021			16.77					$^{2}/_{9}$ 1000+350=650 g. horse-meat, 1590 ccm. water. Diarrhœa.
$^{4}/_{9}$	10.00	750 D.580		1.04	7.85	6.78		1.15	—	—	$^{3}/_{9}$ No food. 1 g. subn. bismuth 600 ccm. water.
$^{5}/_{9}$	9.95	1800 D.1500	1025	3.69	66.42	15.75	1.06	4.21	—	—	$^{4}/_{9}$ 500 g. horse-meat, 1210 ccm. water.
$^{6}/_{9}$	10.00	760 D.560	1015	1.60	12.16	5.16	0.38	2.35	—	—	$^{5}/_{9}$ 100 g. horse-meat, 450 ccm. water, 100 g. fat.
$^{7}/_{9}$	10.00	990 D.700	1012	1.32	14.06	5.26	0.38	2.67	—	—	$^{6}/_{9}$ 100 g. horse-meat, 100 g. fat, 300 ccm. water.
$^{8}/_{9}$	10.00	1100 D.800	1010	0.85	9.35	4.69	0.37	1.99	—	—	$^{7}/_{9}$ 100 g. horse-meat, 100 g. fat, 650 ccm. water.
$^{9}/_{9}$	10.00	865 D.675	1011	1.04	8.99	4.78	0.41	1.88	—	—	$^{8}/_{9}$ 100 g. horse-meat, 100 g. fat, 550 ccm. water.
$^{10}/_{9}$	10.10	660 D.500		1.04	6.86	4.19		1.63	+	—	$^{9}/_{9}$ 100 g. horse-meat, 100 g. fat, 490 ccm. water.
$^{12}/_{9}$	10.15	925 D.725	1006	0.42	3.88	4.17	0.26	0.92	+	—	$^{11}/_{9}$ 100 g. horse-meat, 100 g. fat, 700 ccm. water.
$^{13}/_{9}$	10.50	1100 D.725	1007	1.13	12.43	4.00	0.27	3.10	+	—	$^{12}/_{9}$ 100 g. horse-meat, 100 g. fat, 700 ccm. water.
$^{14}/_{9}$	10.50	690 D.450	1005	0	0	2.53	0.19		+	—	$^{13}/_{9}$ No food, 400 ccm. water.
$^{15}/_{9}$	9.95	980	1005	0	0	2.46	0.19		+	—	$^{14}/_{9}$ 150 g. fat, 590 ccm. water.
$^{16}/_{9}$	10.05	1140 D.825	1004	0	0	2.51	0.22		+	—	$^{15}/_{9}$ 150 g. fat, 900 ccm. water.
$^{17}/_{9}$	10.00	1125 D.950	1004	0	0	3.11	0.42		+	—	$^{16}/_{9}$ 110 g. fat, 1120 ccm. water.
$^{18}/_{9}$	10.10	885 D.710	1008	0.71	6.28	3.80	0.32	1.63	+	—	$^{17}/_{9}$ 100 g. horse-meat, 100 g. fat, 550 ccm. water.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone	Alb.	
19/9	10.05	1480 D.1200	1008	0.71	10.50	5.28	0.49	1.98	+	—	18/9 100 g. horse-meat, 100 g. fat, 1210 ccm. water.
20/9	10.20	940 D.785	1009	0.85	7.99	4.54	0.54	1.78	+	—	19/9 100 g. horse-meat, 100 g. fat, 900 ccm. water.
21/9	10.15	1100 D.1000	1008	0.57	6.27	4.42	0.58	1.41	+	—	20/9 100 g. horse-meat, 100 g. fat, 930 ccm. water.
22/9	10.20	1060 D.865	1007	0.23	2.43	3.71	0.56	0.66	+	—	21/9 100 g. horse-meat, 100 g. fat, 760 ccm. water.
23/9	9.95	2275 D.1075	1006	0.23	5.23	3.66	0.83	1.43	+	—	22/9 100 g. horse-meat, 100 g. fat, 1100 ccm. water.
24/9	10.05	1665 D.1550	1005	0.37	6.16	4.61	0.75	1.33	+	—	23/9 100 g. horse-meat, 100 g. fat, 1540 ccm. water.
26/9	10.00	1270 D.1150	1016	1.60	20.32	7.77	0.92	2.61	+	—	25/9 200 g. horse-meat, 100 g. fat, 1000 ccm. water, withdrawn from the cage.
3/10	9.85	640	1006	0	0						2/10 120 g. fat.
4/10	9.85	870	1005	0	0	1.76	0.40		+	—	3/10 120 g. fat, 800 ccm. water.
5/10	9.80	1560 D.1290	1005	0	0	2.62	0.52		+	—	4/10 120 g. fat, 1420 ccm. water.
6/10	9.50	2220 D.2030	1005	0	0	2.56	0.96		+	—	5/10 120 g. fat, 2050 ccm. water.
7/10	9.50	1960 D.1960	1005	0	0	2.88	1.21		+	—	6/10 120 g. fat, 1960 ccm. water.
8/10	9.30	2620 D.2450	1005	0.19	4.97	4.30	1.58	1.56	+	—	7/10 100 g. horse-meat, 120 g. fat, 2650 ccm. water.
9/10	9.25	2720 D.2690	1005	0.19	5.16	3.80	1.52	1.36	+	—	8/10 100 g. horse-meat, 120 g. fat, 2630 ccm. water.
10/10	9.15	2260 D.1980	1006	0.09	2.03	4.03	1.39	0.50	+	—	9/10 100 g. horse-meat, 120 g. fat, 2020 ccm. water.
11/10	9.30	1900 D.1850	1006	0.14	2.66	3.19	0.84	0.83	+	—	10/10 100 g. horse-meat, 120 g. fat, 1850 ccm. water.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone	Alb.	
12/10	9.50	1700 D.1450	1008	0.61	10.37	5.83	1.31	1.77	+	—	11/10 100 g. horsemeat, 100 g. oxpancreas boiled, 120 g. fat, 1450 ccm. water.
13/10	9.55	1890 D.1800	1006	0.47	8.88	5.22	1.31	1.70	+	—	12/10 100 g. horsemeat, 100 g. boiled oxpancreas, 120 g. fat, 1780 ccm. water.
14/10	9.60	1590 D.1420	1007	0.33	5.24	5.89	1.35	0.80	+	—	13/10 100 g. horsemeat, 100 g. boiled oxpancreas, 120 g. fat, 1210 ccm. water.
15/10	9.70	1410 D.1210	1009	0.38	5.35	5.92	1.37	0.90	+	—	14/10 200 g. horsemeat, 120 g. fat, 1100 ccm. water.
16/10	9.75	1280 D.1020	1009	0.52	6.65	5.10	1.26	1.30	+	—	15/10 200 g. horsemeat, 120 g. fat, 900 ccm. water.
17/10	9.85	1320 D.1070	1009	0.52	6.86	5.22	1.23	1.31	+	—	16/10 200 g. horsemeat, 120 g. fat, 1030 ccm. water.
18/10	9.95	1440 D.1290	1010	0.66	8.71	5.94	0.99	146	+	—	17/10 100 g. horsemeat, 100 g. fresh oxpancreas, 120 g. fat, 1230 ccm. water.
19/10	10.05	1540 D.1380	1008	0.47	7.23	5.49	0.95	1.31	+	—	18/10 100 g. horsemeat, 100 g. fresh oxpancreas, 120 g. fat, 1390 ccm. water.
20/10	10.15	1420 D.1200	1010	0.80	11.36	6.01	1.55	1.87	+	—	19/10 100 g. horsemeat, 100 g. fresh oxpancreas, 120 g. fat, 1220 ccm. water.
21/10	10.15	1415 D.1300	1010	0.75	10.61	5.44	1.39	1.95	+	—	20/10 200 g. horsemeat, 120 g. fat, 1240 ccm. water.
22/10	10.20	1540 D.1390	1010	0.99	15.24	5.44	1.57	2.88	+	—	21/10 200 g. horsemeat, 120 g. fat, 1200 ccm. water.

Date	Weight kg.	Urine									Remarks
		Quant. ccm.	Sp G.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	Acetone	Alb.	
23/10	10.20	2200 D.1900	1008	0.66	14.52	6.16	1.75	2.35	+	—	22/10 200 g. horsemeat, 120 g. fat, 1800 ccm. water.
24/10	10.25	1735 D.1600	1009	0.94	16.30	6.41	1.62	2.54	+	+	23/10 200 g. horsemeat, 120 g. fat, 1580 ccm. water.
25/10	10.15	2000 D.1900	1009	0.66	13.20	7.07	1.93	1.86	+	+	24/10 200 g. horsemeat, 120 g. fat, 1800 ccm. water.
28/10	10.10	2150 D.2150	1009	0.75	16.10				+	+	27/10 200 g. horsemeat, 120 g. fat, 2100 ccm. water.
26/2	8.90										25/2 500 g. horsemeat, 50 g. fat.
27/2	8.90	1360	1028	3.60	48.96	15.47		3.16	1.81	+	26/2 500 g. horsemeat, 50 g. fat, 1120 ccm. water.
28/2	9.00	1140	1027	3.69	40.06				1.06	+	27/2 500 g. horsemeat, 50 g. fat, 1090 ccm. water.
1/3	8.80	930	1033	4.16	38.68				1.17	+	28/2 500 g. horsemeat, 50 g. fat, 680 ccm. water.
2/3	8.75	1200	1030	3.60	43.20	16.21	2.48	2.66	1.53	+	1/3 500 g. horsemeat, 50 g. fat, 1 g. hypophysis, 890 ccm. water.
3/3	8.65	1260	1027	3.03	38.17	13.45	2.63	2.83	1.60	+	2/3 500 g. horsemeat, 50 g. fat, 1 g. hypophysis, 990 ccm. water.
4/3	8.70	1380	1025	2.55	35.19	14.49	2.69	2.42	1.27	trace	3/3 500 g. horsemeat, 50 g. fat, 1 g. hypophysis, 1190 ccm. water.
5/3	8.70	1150	1027	3.17	35.45	14.20	2.70	2.49	1.02	trace	4/3 500 g. horsemeat, 50 g. fat, 980 ccm. water.
6/3	8.80	1330	1026	2.93	38.96	14.72	2.52	2.64	1.06	trace	5/3 500 g. horsemeat, 50 g. fat, 1120 ccm. water.
7/3	8.80	1170	1028	2.79	32.64				0.77	+	6/3 500 g. horsemeat, 50 g. fat, 800 ccm. water.

Date	Weight kg.	Urine							Remarks.
		Quant. ccm.	Sp g.	Glucose %	Glucose g.	N g.	NH_3 g.	D/N	
8/3	8.70	730	1038	4.30	31.39				7/3 500 g. horse-meat, 50 g. fat, 550 ccm. water.
9/3	8.55	900	1035	4.16	37.44				8/3 500 g. horse-meat, 50 g. fat, 730 ccm. water.
10/3	8.50	840	1034	4.07	34.18				9/3 500 g. horse-meat, 50 g. fat, 650 ccm. water.
11/3	8.40	930	1028	3.60	33.48				10/3 500 g. horse-meat, 50 g. fat, 640 ccm. water.
12/3	8.40	850	1029	3.60	30.60				11/3 500 g. horse-meat, 50 g. fat, 600 ccm. water.
13/3	8.40	740	1033	3.60	26.64				12/3 500 g. horse-meat, 50 g. fat, 510 ccm. water.

The dog is now utilised for experiments regarding the effect of alcohol on acidosis and ketonuria. (In collaboration with H. SALVESEN. Results published elsewhere). During these experiments the dog continued to lose flesh steadily. On 24/4 it weighed 8.00 kg., on 1/5 7.53 kg., on 12/5 6.90 kg. Cataract occurred. The dog became very feeble. During the last days of the experiment in the cage it had respiratory difficulties. It was therefore put into the kennel and received a diet rich in carbo-hydrates (dog-biscuits and some bread). It ate some of this, but became more and more feeble. It lived 2 days more (after being taken out of the cage and after the beginning of the carbo-hydrate diet). It died quietly on the afternoon of 31/5 without any appearance of coma. No respiratory troubles in the last days. The urine for the last days was not collected.

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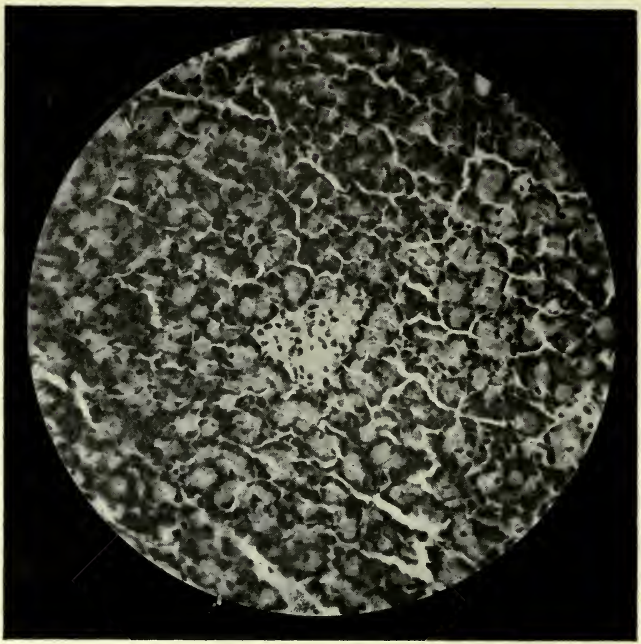

Fig. I. Pancreas from a normal dog with one island of Langerhans. × 190.

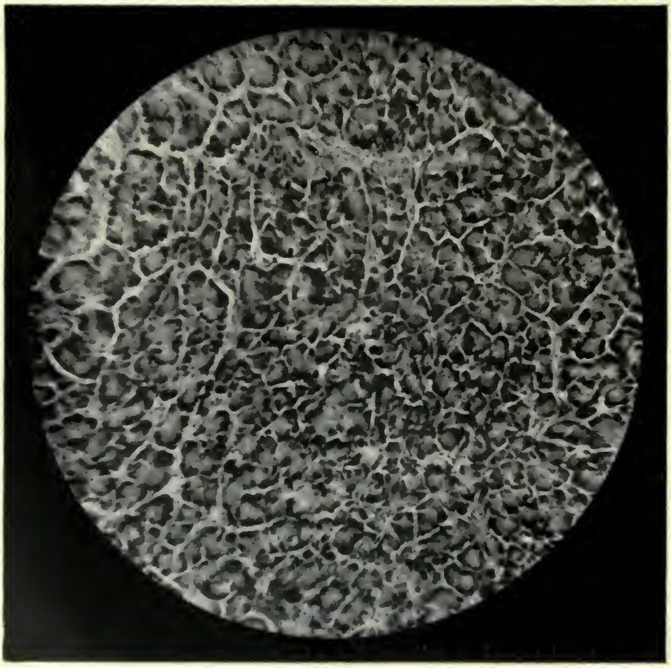

Fig. II. Pancreas from a diabetic dog (Dog 1). — Infiltration of connective tissue. Secreting acini, no islands of Langerhans. × 190.

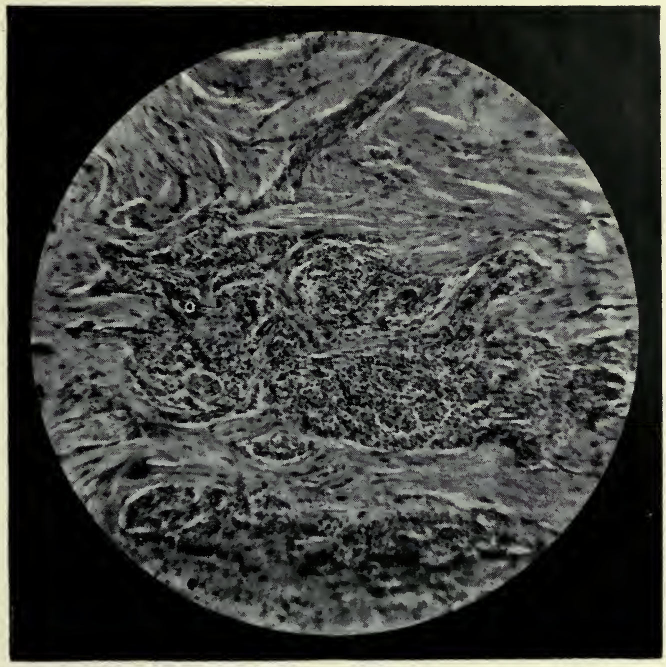

Fig. III. Pancreas from partially depancreatised dog without diabetes (Dog II). Proliferation of tissue of islands of Langerhans, surrounded by sclerotic connective tissue. No acini. × 60.

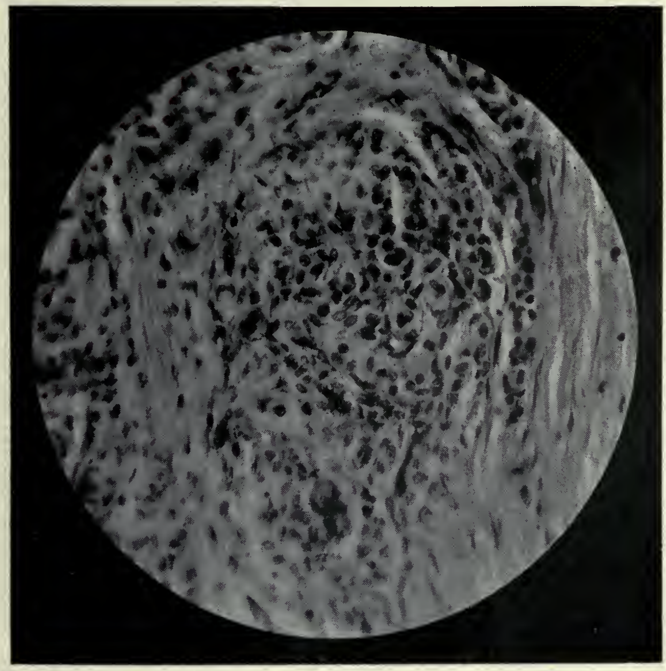

Fig. IV. Pancreas from partially depancreatised dog without diabetes (Dog II). Extreme proliferation of tissue of Langerhans-islands. (Same picture as in Fig. III, more highly magnified) × 260.

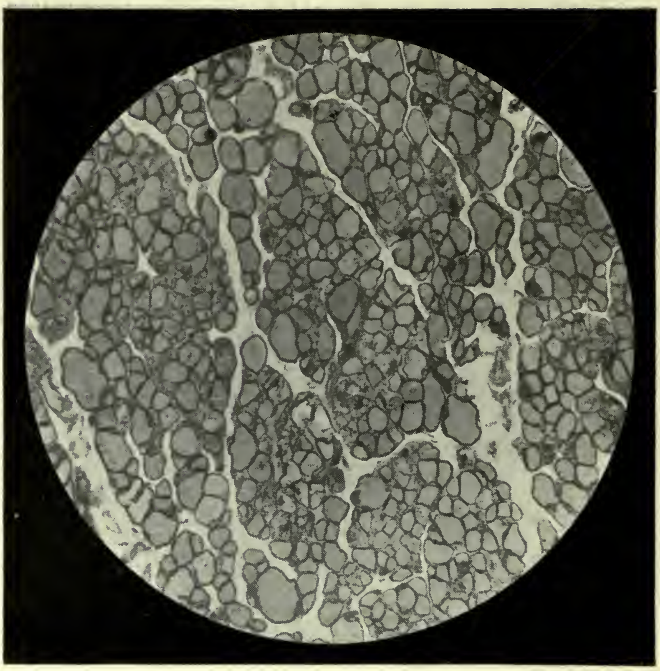

Fig. V. Thyreoidea from a normal dog × 20.

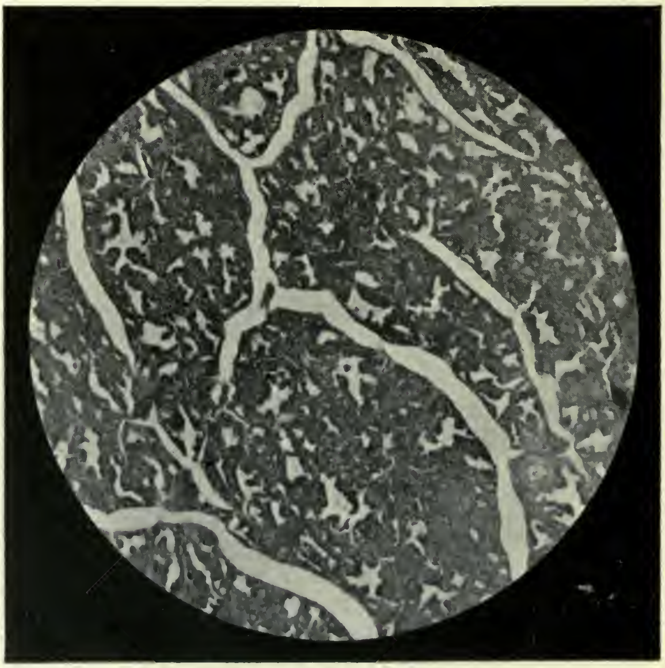

Fig. VI. Hypertrophied thyreoidea from partially depancreatised dog without diabetes (Dog II). Extreme proliferation of the epithelium with formation of compact groups of cells. Alveoli small and irregular with scanty colloid-content. × 20.

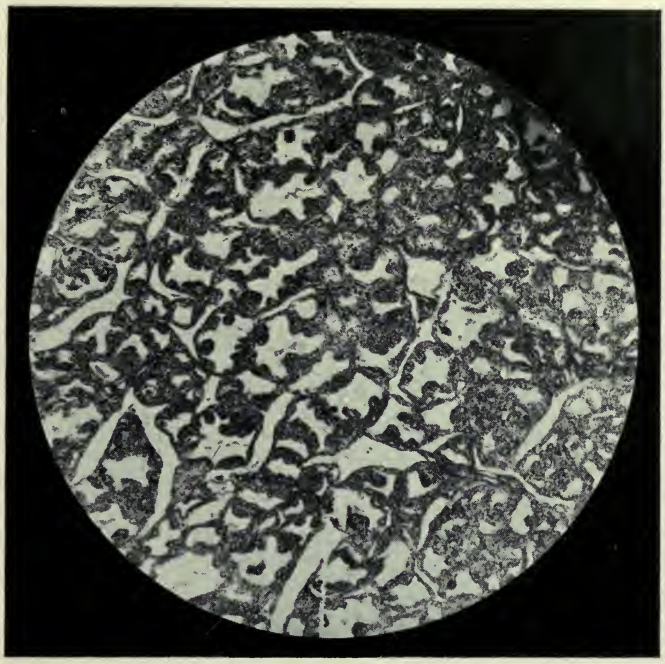

Fig. VII. Hypertrophied thyreoidea from partially depancreatised dog without diabetes (Dog III). Irregular proliferation of the epithelium. The cell-groups not quite so compact as in Fig. VI. × 20.

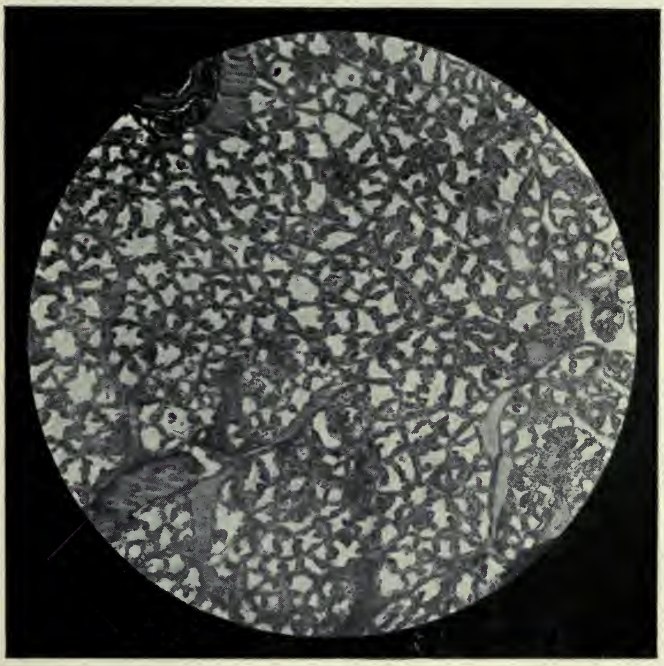

Fig. VIII. Hypertrophied thyreoidea from diabetic dog (Dog I). Proliferation of the epithelium. Alveoli irregular with scanty colloid-content × 20.

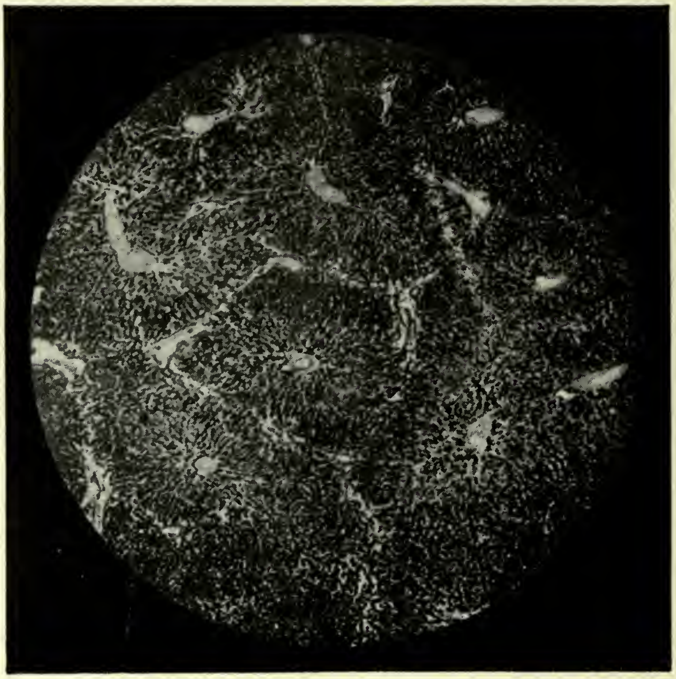

Fig. IX. Fat-infiltrated liver from diabetic dog. (Dog I) Sudan × 25.

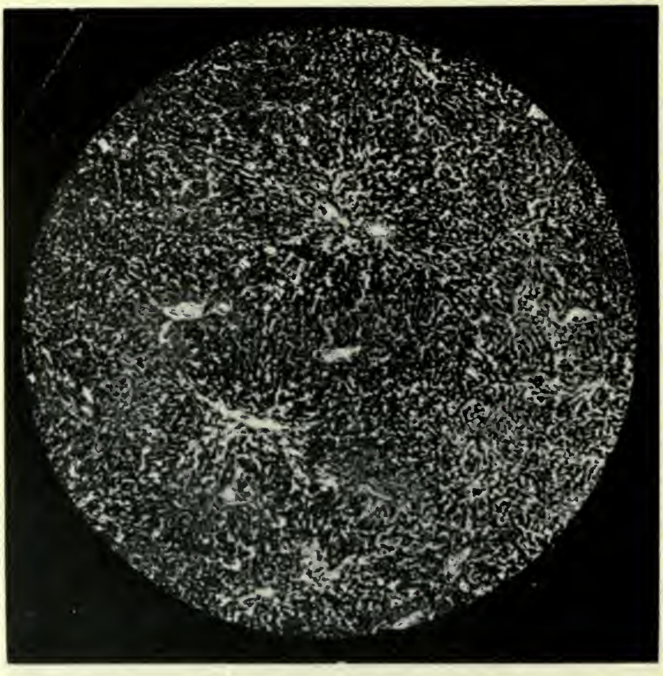

Fig. X. Fat-infiltrated liver from diabetic dog (Dog IV) Sudan × 25.

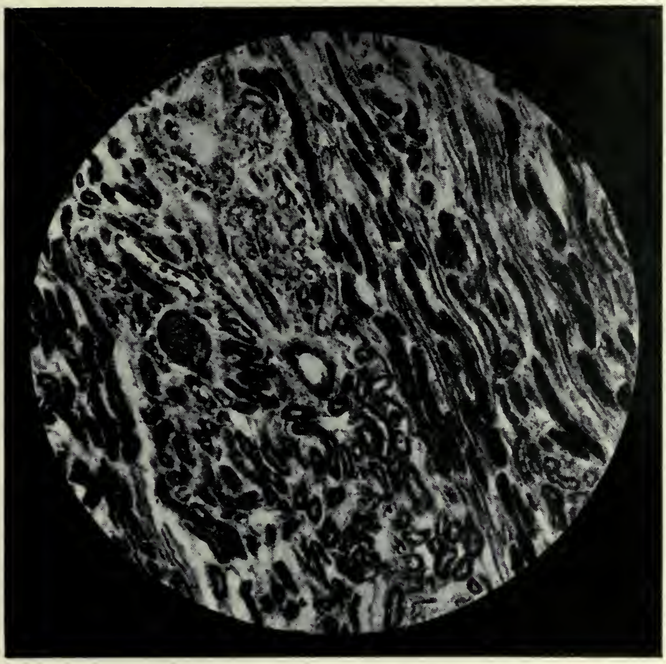

Fig. XI. Fat-infiltrated kidney from diabetic dog (Dog I) Sudan × 25.

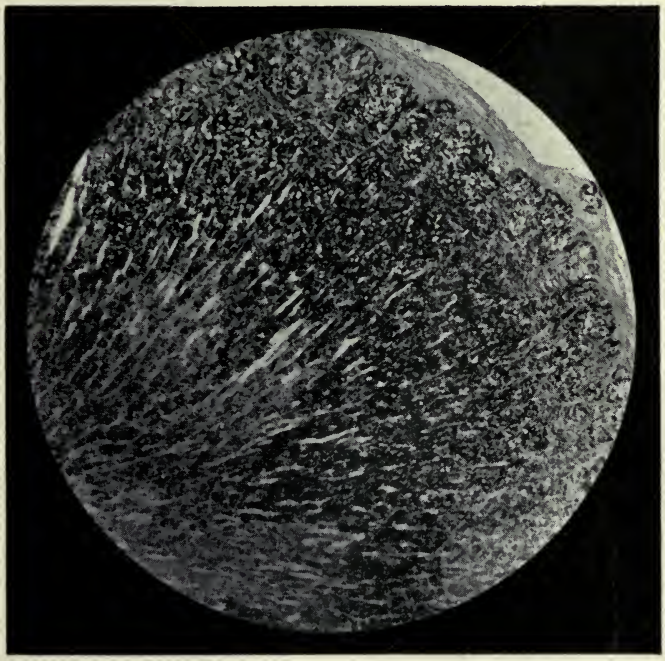

Fig. XII. Adrenal gland from diabetic dog (Dog I). Enlargement of lipoid granules in the cortex. In many places these granules have gathered together so as to form drops, which appeared as cavities in the paraffin preparation, as is also sometimes the case in this preparation. Sudan × 50.

Stockholm 1920. P. A. Norstedt & Söner.